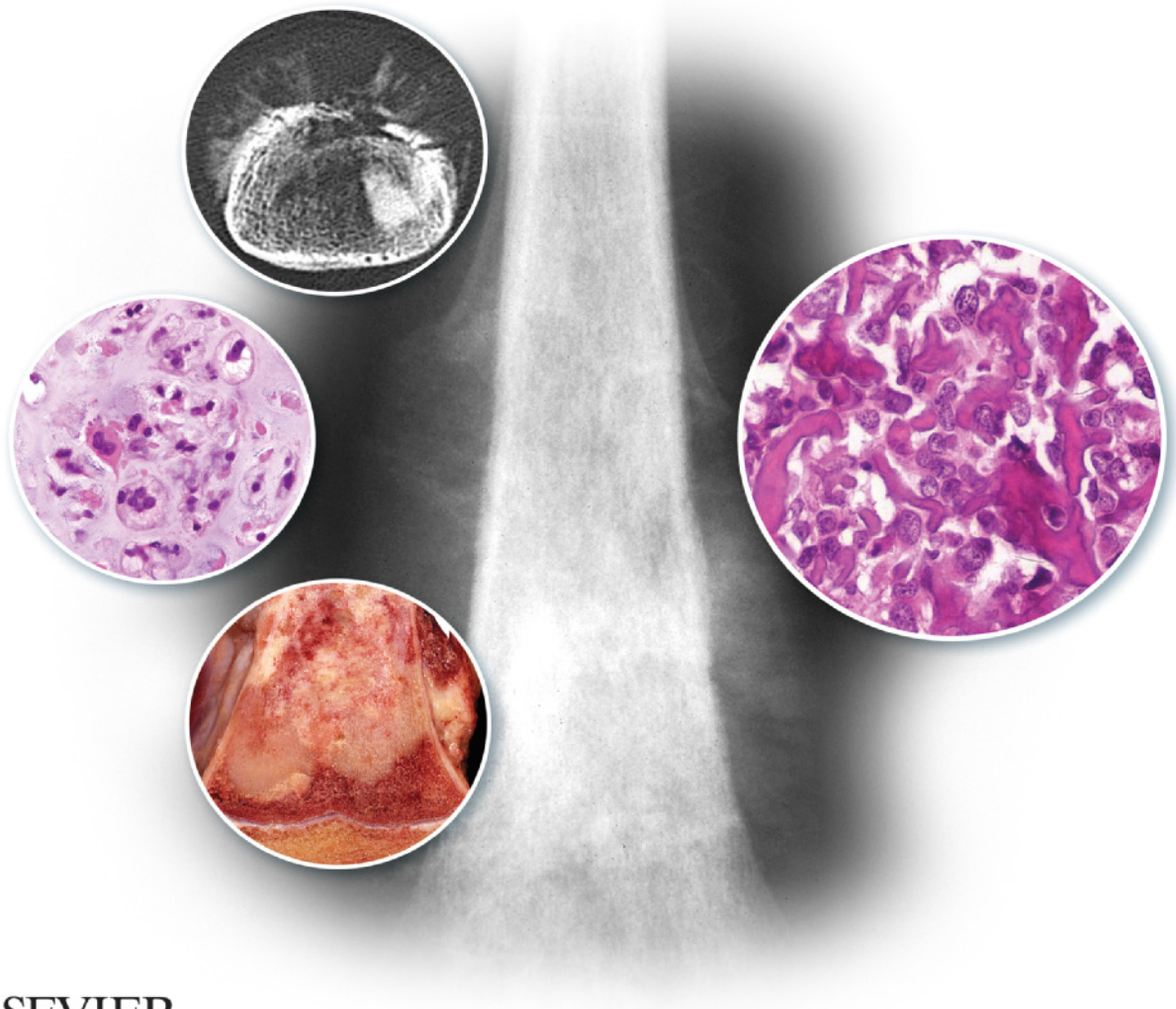
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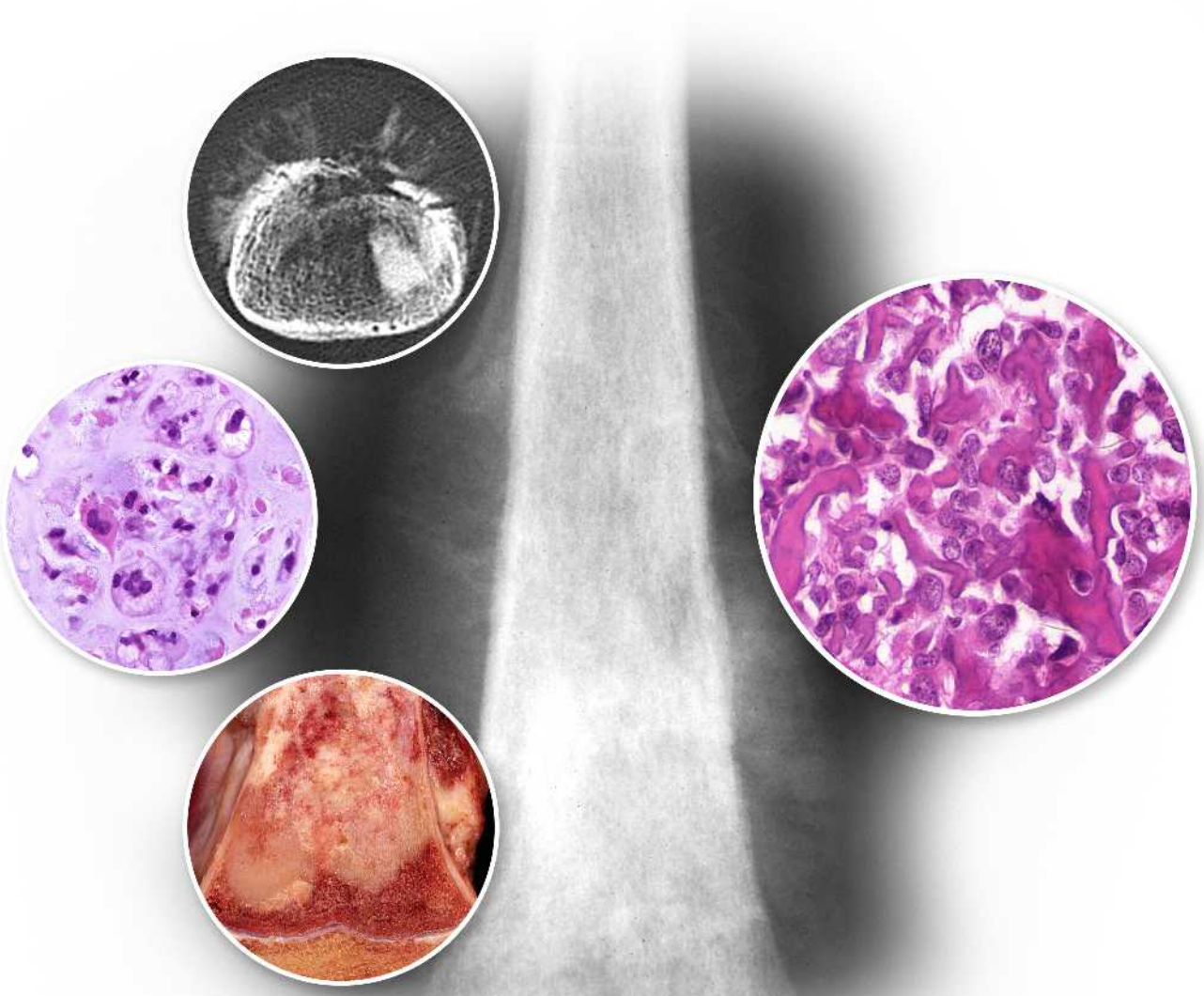
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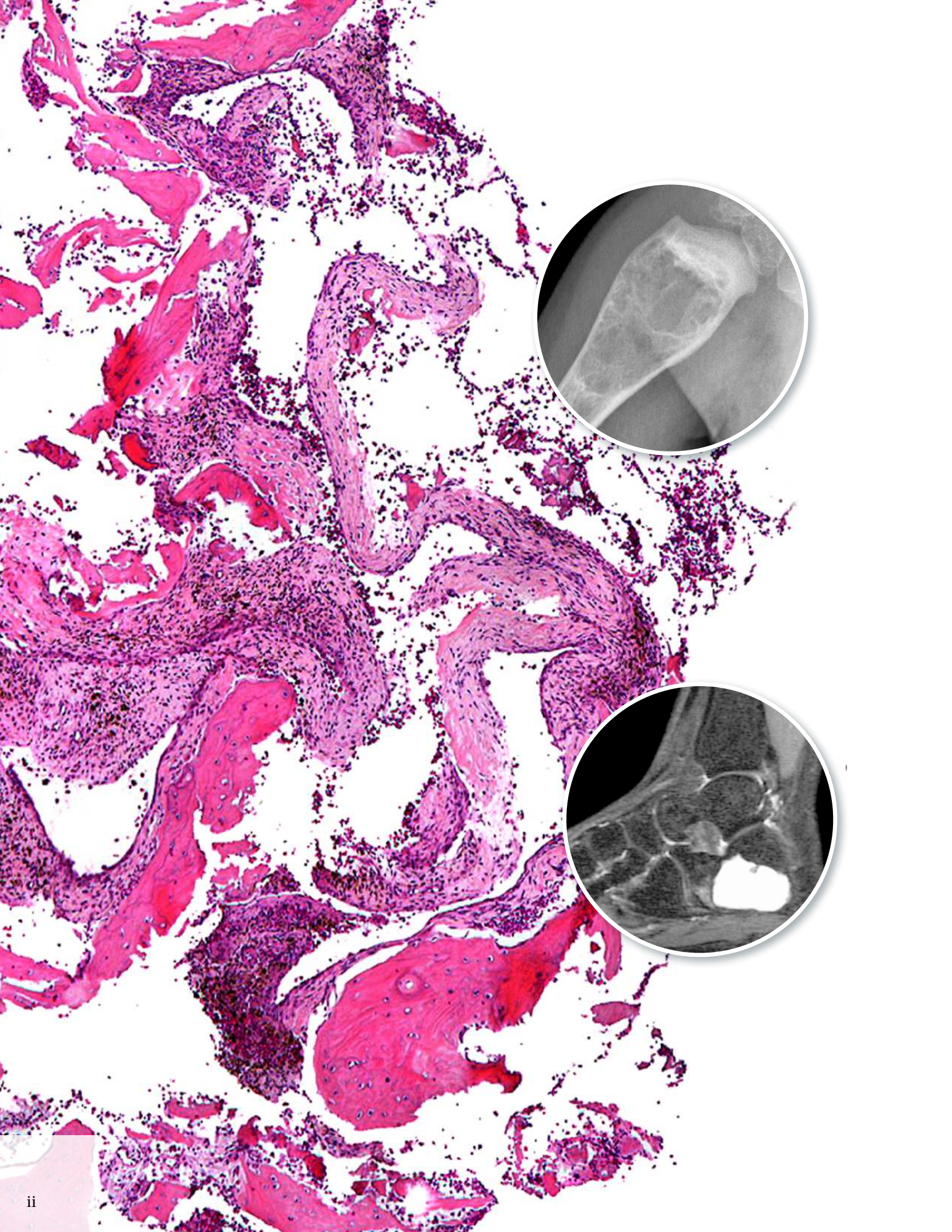
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DIAGNOSTIC PATHOLOGY

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# Dedications

*To my wife and family.*

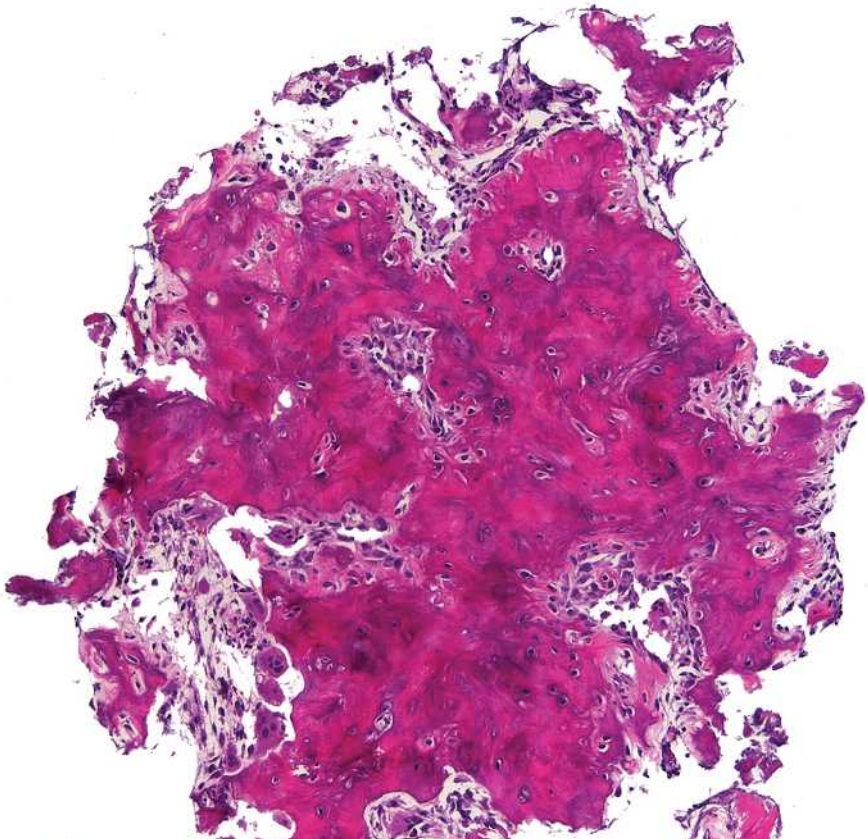
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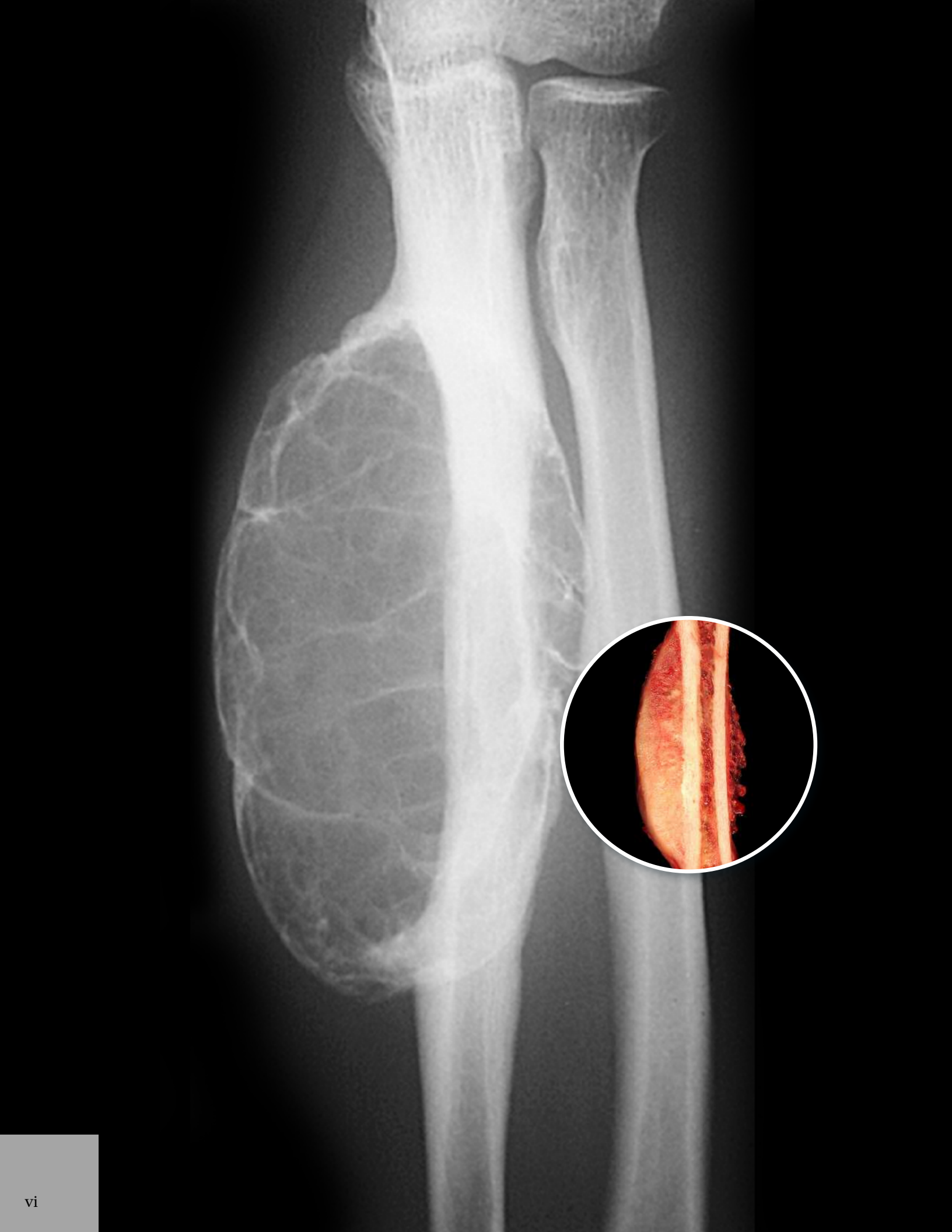
*To my daughters, Olivia and Miranda, who are my lifelong joy; my parents, Philip and Evelyn, who did their best; my siblings, David, Stuart, and Elaine, who have been supportive; my friend and colleague, Al, who always has my back; my teachers who have helped show me the way; my colleagues with whom I have had the honor to be in the trenches; and the patients who have given me their trust.*

**AER**

*To my father, Dhirendra, and mother, Shashi.*

**VD**





# Preface

The pathology of the skeleton is complex and is the morphologic expression of a broad spectrum of diseases, including those caused by genetic (sporadic and inherited), malformative, inflammatory, metabolic, circulatory, traumatic, iatrogenic, and neoplastic disorders. Bone tumors, including both neoplasms and various conditions that may simulate them, are the focus of our book. This topic is one of the most challenging areas in surgical pathology for several reasons: Bone tumors are uncommon, making it difficult to acquire the necessary experience with their histological variants and mimics; the correct diagnosis usually requires the careful integration of radiological imaging studies and clinical findings; the implications of a diagnosis on a patient can be life changing; and medical schools and pathology training programs often have insufficient expertise to provide medical students and young pathologists with the skills needed to diagnose these lesions accurately and precisely.

This book reflects the philosophy and high standards practiced by the truly multidisciplinary team of physicians at the Massachusetts General Hospital and University of Miami, who have diagnosed and surgically treated tens of thousands of patients with bone tumors for many decades. Also important to acknowledge are the contributions of the many fellows and residents who participated in the efforts of patient care.

The authors are subspecialized physicians who have dedicated their professional lives to the diagnosis and surgical management of bone tumors. As a result, the figures include beautiful and classic examples and unusual variants of many of the diseases discussed and are the product of painstaking correlations between the clinical, imaging, macroscopic, histological, immunohistochemical, and molecular characteristics of bone tumors. The text synthesizes the literature and our combined extensive experience, and the images have been selectively culled from the patient files of the Massachusetts General Hospital, the University of Miami Miller School of Medicine, and the private consultations of the authors. The book is constructed in a thematic format with sections representing groups of related diseases and the chapters discussing individual entities and their differential diagnosis.

Accordingly, this textbook serves as an excellent resource for medical students, residents, fellows, and practicing physicians in the disciplines of pathology, radiology, and orthopedics. Medical and radiation oncologists who treat bone tumors will also find it valuable. Our opportunity to participate in the care of patients with bone tumors has been our call and honor, and we hope to do it justice by sharing our experience with the medical community—our goal is to enhance diagnostic accuracy and to provide the biological basis for optimal treatment.

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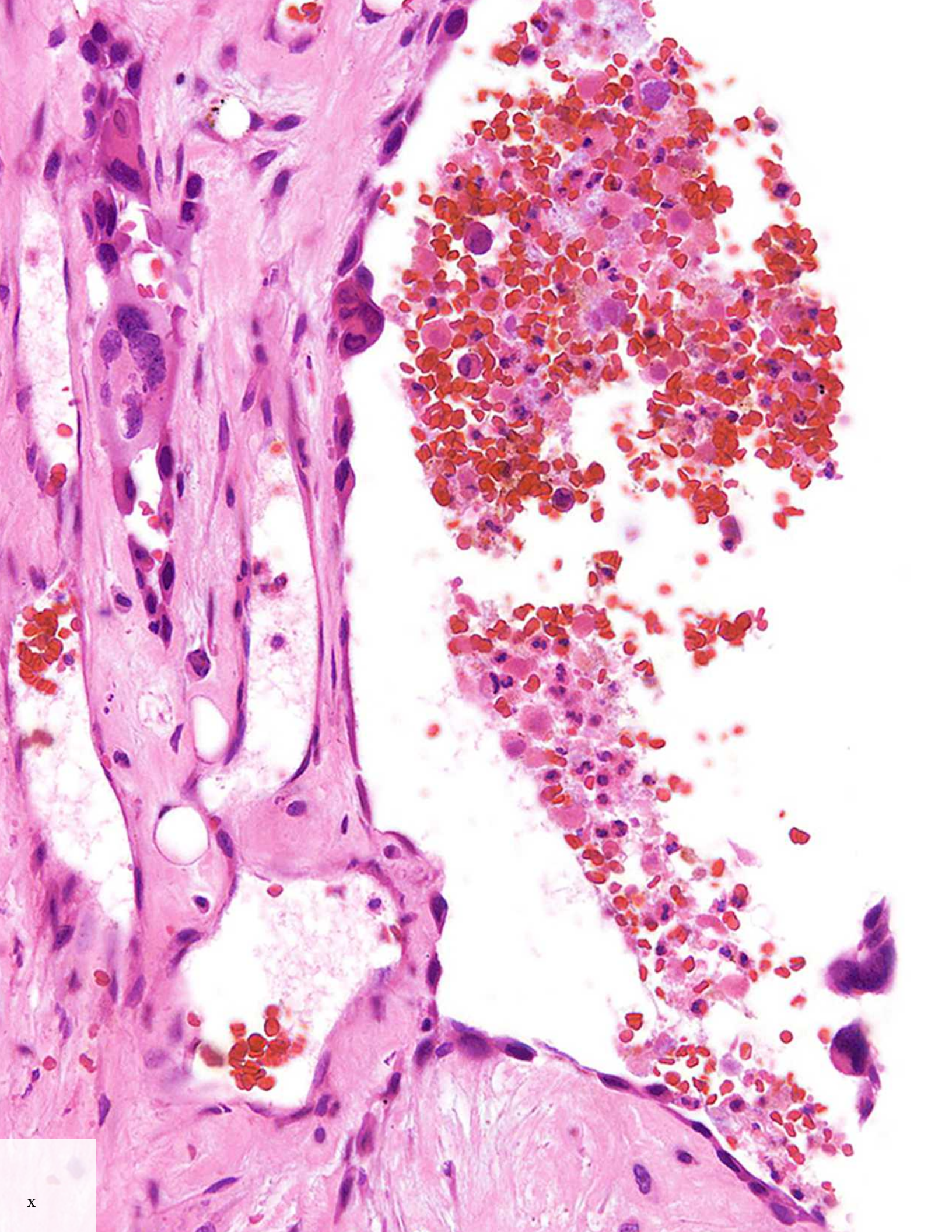
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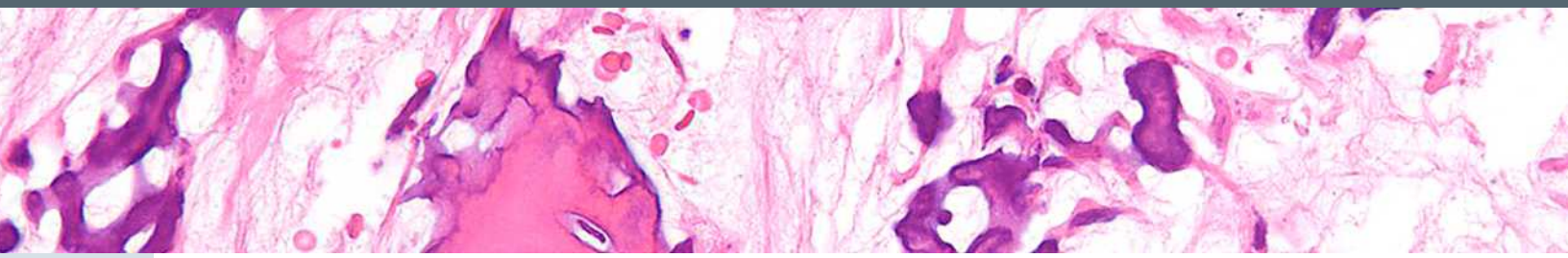
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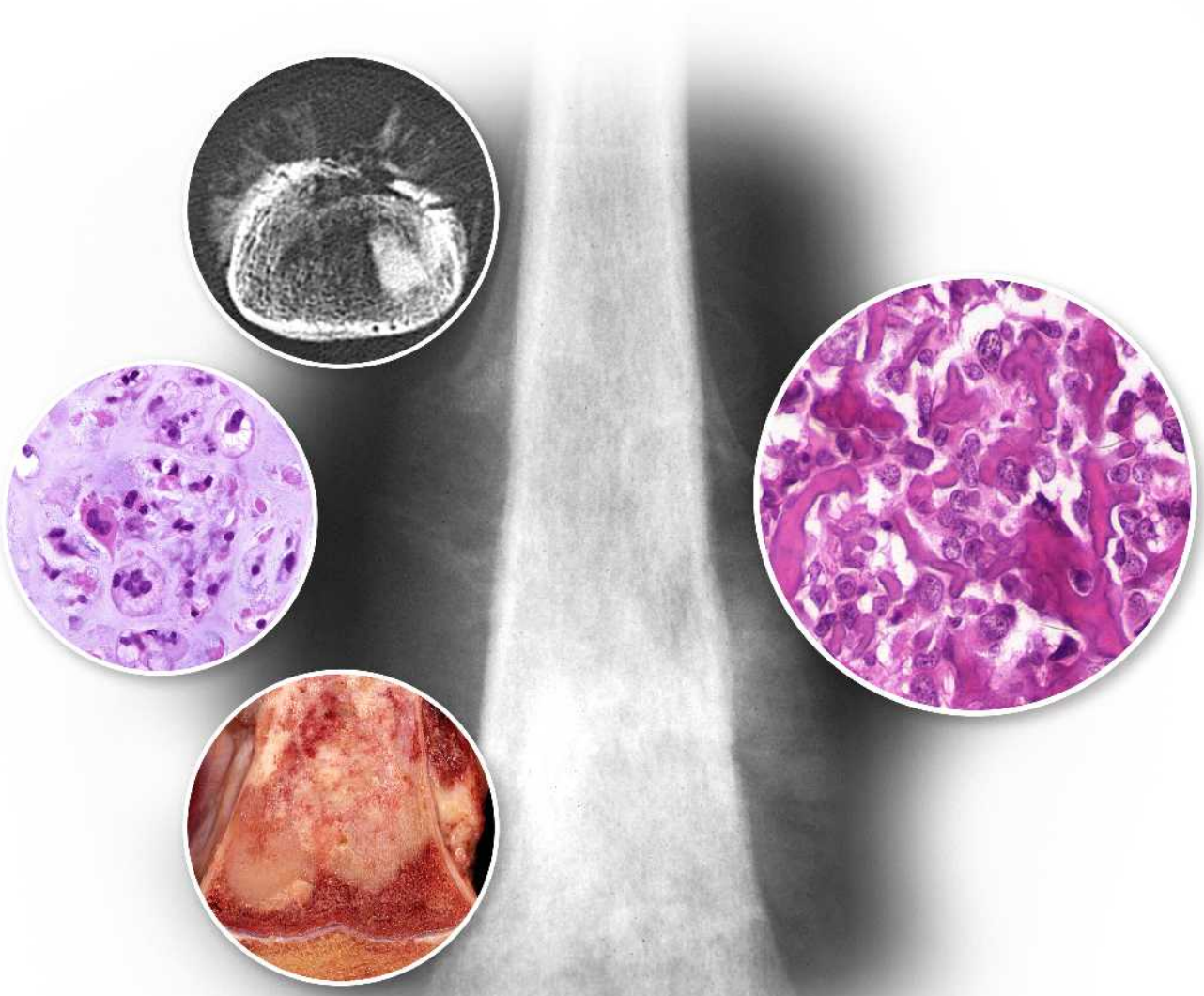
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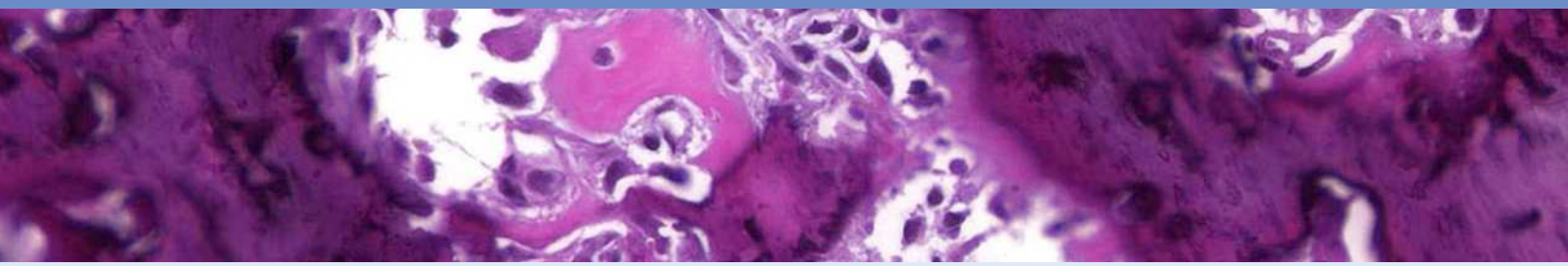
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SECTION 1

# Benign Bone-Forming Tumors




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KEY FACTS

## TERMINOLOGY

- Enostosis

## CLINICAL ISSUES

- Incidental radiographic finding
- Large bone islands in children may be concerning for osteosarcoma
- Rarely need to be biopsied
- Multiple bone islands represent osteopoikilosis
- Observation for small solitary characteristic lesions, but those that are large or have unusual features may require biopsy

## IMAGING

- Most frequent sites include pelvis, proximal femur, and ribs
- In osteopoikilosis, usually involve epiphyses of short tubular bones
- Generally not much larger than 1 cm in diameter
- Homogeneously radiodense lesions with spiculated margins, which merge with surrounding cancellous bone

## MACROSCOPIC

- Hard, solid, tan-white
- Periphery blends with surrounding cancellous bone

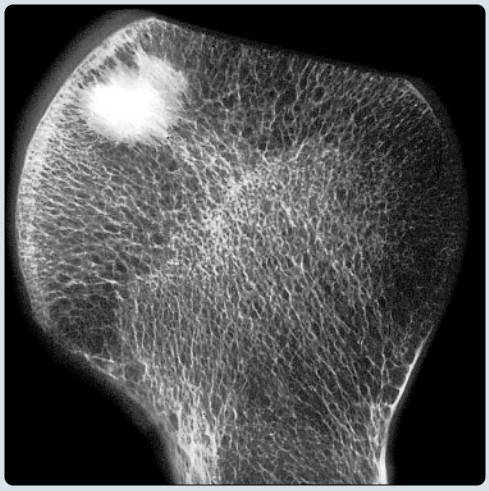
## MICROSCOPIC

- Consist of cortical-type bone containing haversian-like canals
- Predominately lamellar but may be focally woven
- Osteopoikilosis bone island tumors are identical to sporadic, solitary bone islands

## TOP DIFFERENTIAL DIAGNOSES

- Well-differentiated osteosarcoma
- Sclerotic metastases

**Specimen Radiograph of Bone Island**

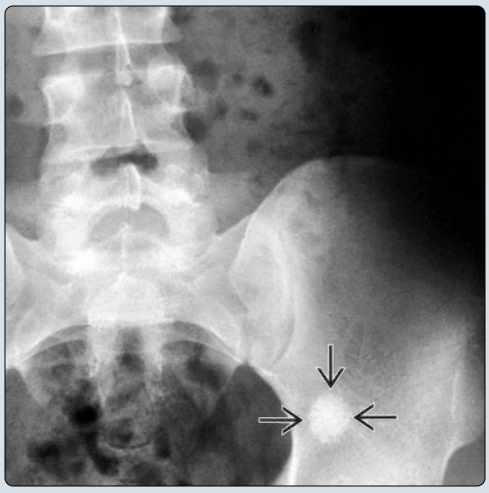


**Gross Photograph of Bone Island**



**(Left)** *Specimen radiograph shows excised femoral head containing a bone island. The bone island is oval and radiodense. The periphery has a stellate margin merging with the neighboring cancellous bone.* **(Right)** *Gross photograph of femoral head shows bone island beneath the articular surface. The bone island is dense, tan-white, and has a spiculated border as it merges with the adjacent bony trabeculae.*

**Bone Island Involving Pelvis**



**CT Scan of Pelvic Bone Island**



**(Left)** *Radiograph of the pelvis demonstrates a uniformly dense bone island. The spiculated margins represent extensions from the lesion, which merge with the surrounding cancellous bone.* **(Right)** *CT of a bone island demonstrates that it is of the same density as cortical bone. The absence of a lytic component can be difficult to confirm without additional cross-sectional imaging, an important feature to distinguish bone island from other, more sinister bone-forming lesions.*

## TERMINOLOGY

### Synonyms

- Enostosis
- Spotted bone disease

### Definitions

- Benign bone-forming tumor composed of cortical-type bone that develops within medullary cavity
- Osteopoikilosis
  - Syndrome characterized by presence of multiple (usually many) bone islands
  - Can be associated with Buschke-Ollendorff syndrome and melorheostosis-like lesions

## ETIOLOGY/PATHOGENESIS

### Neoplasm

- Cause of bone island is unknown
- Osteopoikilosis may be inherited in autosomal dominant fashion
  - Associated with mutations and loss of function in *LEMD3* located on 12q14

## CLINICAL ISSUES

### Presentation

- Incidental radiographic finding and asymptomatic
  - Large bone islands may be painful
- Uncommon in children
- Lesions in osteopoikilosis may undergo slow, progressive enlargement or involution

### Treatment

- Observation for small solitary lesions with classic radiographic features
- Larger variants or cases in adolescents may require biopsy to exclude more aggressive lesions, such as well-differentiated osteosarcoma and sclerotic metastases in adults

### Prognosis

- Excellent
- Malignant transformation does not occur

## IMAGING

### General Features

- Location
  - Most frequent sites are pelvis, ribs, and proximal femur
  - In adults, incidence in pelvic bones (1.0%) and ribs (0.5%)
  - Epiphyseal in tubular bones
  - Osteopoikilosis is bilateral and symmetrical in distribution and in metaphyseal and epiphyseal regions of tubular bones
    - Any bone may be affected, including tarsal and carpal bones
- Size
  - Usually < 1 cm in diameter
  - Infrequently, "giant" bone islands several cm in diameter occur

### Radiographic Findings

- Small
- Oval
  - Long axis of oval is usually parallel to mechanical stresses on bone, representing adaptation to Wolff law
- Single or multiple
- Larger variants may abut or be based on endosteal surface
  - Do not involve cortex and do not elicit periosteal reaction
- Homogeneously radiodense lesions with spiculated margins that merge with surrounding cancellous bone

### MR Findings

- Dark on T1WI and T2WI, similar to normal cortical bone

### CT Findings

- Small stellate medullary lesion with characteristics of cortical-type bone

### Bone Scan

- Can show some uptake of radionuclide

## MACROSCOPIC

### General Features

- Hard, solid, and tan-white; periphery blends into surrounding trabeculae, which accounts for irregular spiculated margins

## MICROSCOPIC

### Histologic Features

- Consist of cortical-type bone containing haversian-like canals
- Predominately lamellar but may be focally woven
- Osteoblasts lining surfaces are flat and quiescent
- Osteocytes are small and cytologically banal
- Bone islands in osteopoikilosis are identical to sporadic, solitary bone islands

## DIFFERENTIAL DIAGNOSIS

### Well-Differentiated Osteosarcoma

- Infiltrative, composed of proliferating mildly atypical spindle cells and woven bone

### Sclerotic Metastases

- Usually in adults and contain histologically malignant cells

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Multiple lesions raise differential diagnosis of blastic metastases; multiple bone islands seen in osteopoikilosis

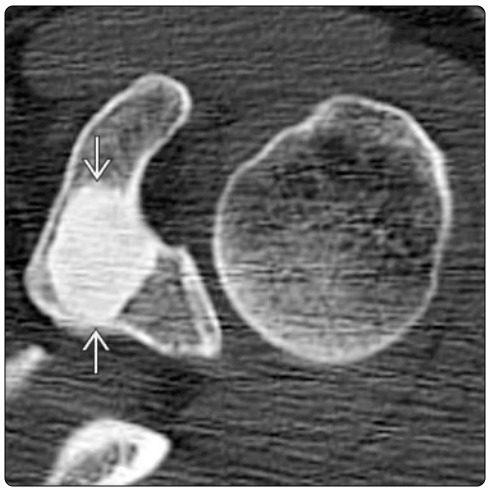
### Pathologic Interpretation Pearls

- Lesion is intramedullary, cortical in type, and predominately lamellar in architecture

## SELECTED REFERENCES

1. Korkmaz MF et al: Osteopoikilosis: report of a familial case and review of the literature. Rheumatol Int. ePub, 2014

**CT Scan of Bone Island**

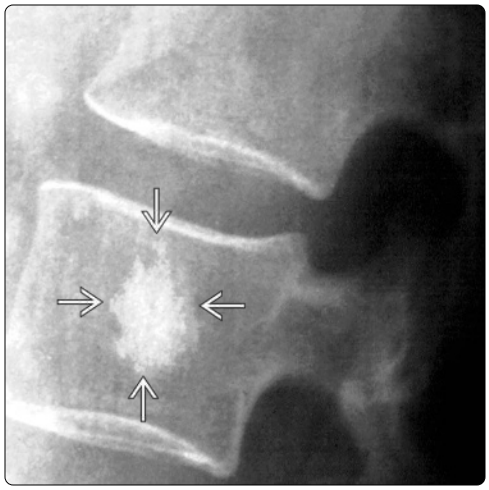


**MR of Bone Island**

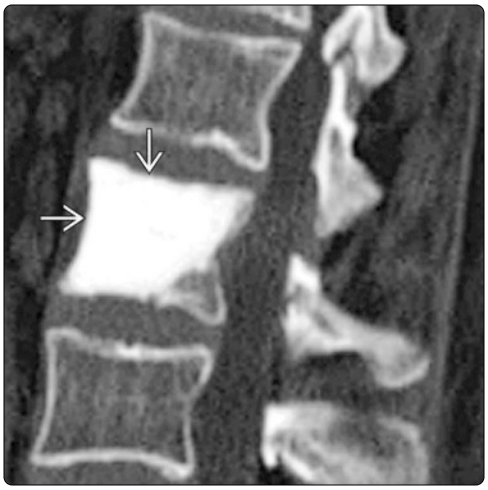


**(Left)** *CT scan of the shoulder demonstrates a very large bone island ➡ of the scapula at the base of the coracoid process. The lesion is uniformly and completely dense and abuts the cortex but does not invade or transgress it.* **(Right)** *MR of a round bone island ➡ shows that it is uniformly hypointense and abuts the cortex but does not invade or transgress it. The marrow adjacent to the ossified lesion is completely normal.*

**Bone Island of Spine**

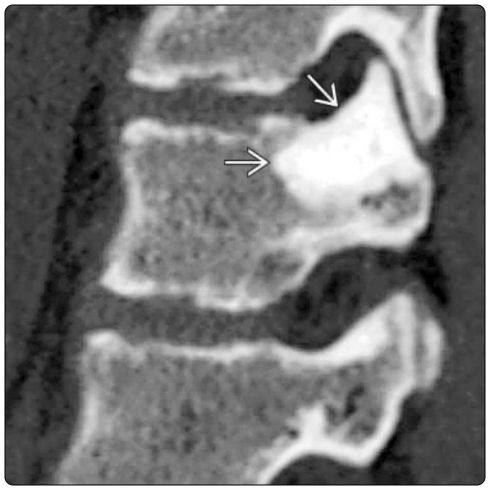


**Bone Island of Spine**

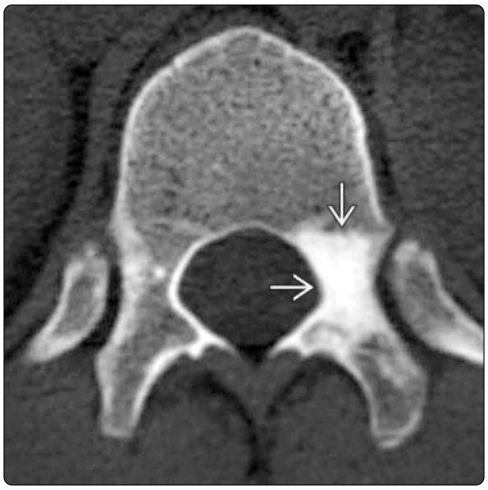


**(Left)** *A bone island of the central portion of the vertebral body shows characteristic features: Uniform density and spiculated margins ➡. The lesion is surrounded by unremarkable cancellous bone, and the cortex is uninvolved.* **(Right)** *A giant bone island of the vertebra is shown ➡ almost filling the entire vertebral body. Such large lesions can show uptake on isotope bone scans due to their size. In other respects, the features are similar to conventional bone islands.*

**Bone Island Involving Pedicle**

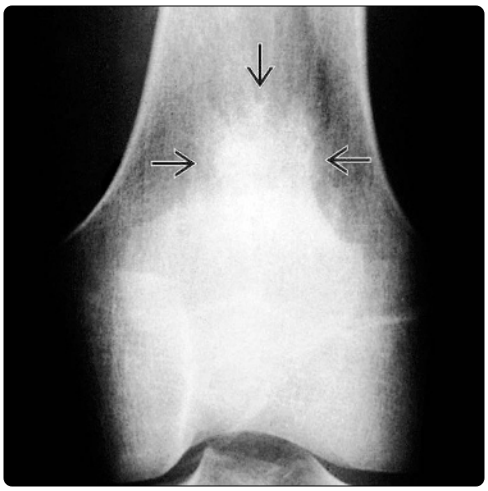


**Bone Island of Pedicle**



**(Left)** *Sagittal CT scan shows a large bone island involving the pedicle and facet joint of T12 ➡. The lesion fills a significant portion of the medullary cavity and merges with the overlying cortex. The intramedullary margin is undulating and focally spiculated. Smaller lesions are seen in the adjacent vertebra.* **(Right)** *Axial CT of a large bone island involves the pedicle and facet joint of T12 ➡. The tumor has the same density as the cortex, which is unremarkable.*

Large Bone Island of Femur



Large Bone Island of Femur



**(Left)** *AP radiograph of the distal femur demonstrates a large bone island involving the metaphysis ⇨. Note the spiculated margin proximally. In this particular lesion, the elongated shape of the lesion is apparent, representing adaptation to mechanical stresses.* **(Right)** *Lateral radiograph of the distal femur demonstrates a large bone island of the posterior portion of the bone ➡. The lesion appears to be based on the endosteal surface and extends into the medullary cavity.*

CT of Bone Island of Femur



Bone Scan



**(Left)** *Axial CT shows a giant bone island of the distal femur ➡ with uniform density of compact bone and spiculated margins. The broad base of the tumor is attached to the endosteal surface of the posterior cortex.* **(Right)** *Isotope bone scan shows a small amount of uptake ➡ in the lateral aspect of the right proximal humerus. A small amount of uptake can be present in bone islands because they are actively bone forming. It should not be considered a marker of malignancy.*

Large Bone Island of Proximal Humerus



MR of Bone Island of Humerus



**(Left)** *CT scan demonstrates a large bone island of the proximal humerus ➡. The lesion is eccentric, abuts the endosteal surface of the cortex, and extends in the medullary cavity in an irregular fashion.* **(Right)** *Coronal T1-weighted MR of the bone island of the humerus demonstrates the homogeneous low signal intensity of the lesion ⇨. The bone island is based on the inner surface of the cortex and has irregular margins. The adjacent marrow is unremarkable.*

**(Left)** *AP radiograph demonstrates osteopoikilosis with multiple bone islands involving the ends of the short tubular bones. The small lesions cluster at the ends of the bones.* **(Right)** *AP radiograph of the knees shows the typical features of osteopoikilosis. A large number of small bone islands are symmetrically distributed in a primarily juxtaarticular and metaphyseal distribution. Despite their multiplicity, each lesion individually has the features typical of a bone island.*

**Osteopoikilosis**



**Osteopoikilosis**



**(Left)** *Reformatted coronal CT scan of the hip shows multiple small bone islands that are juxtaarticular and metaphyseal in distribution. Each lesion is individually indistinguishable from a solitary bone island.* **(Right)** *T1-weighted MR of the knee in a patient with osteopoikilosis demonstrates that the bone islands are small, rather uniform in size, oval in shape, and uniformly dense. Each lesion is individually indistinguishable from a solitary bone island.*

**Osteopoikilosis**



**MR of Osteopoikilosis**

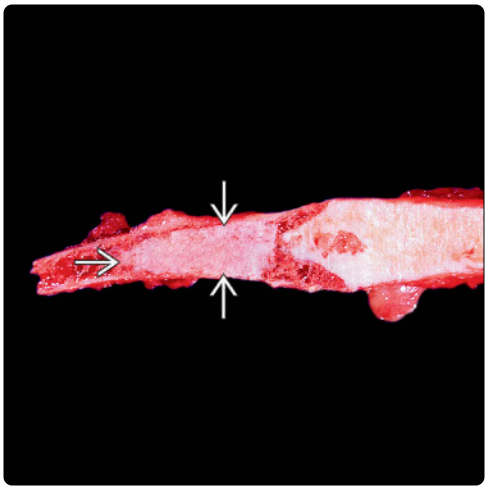


**(Left)** *Coronal CT demonstrates an intramedullary bone island involving the right mandible ⇨. The lesion is sclerotic with the same density as the surrounding cortex.* **(Right)** *Gross photograph shows rib and adjacent costal cartilage. An elongate, dense, and tan-white bone island fills the involved segment of the medullary cavity ⇨. The adjacent cortex and costal cartilage are unremarkable.*

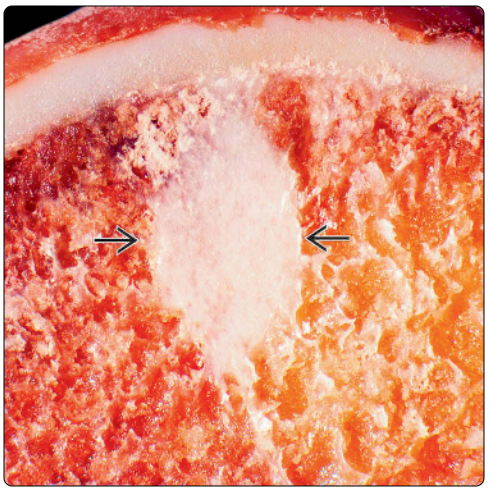
**Bone Island of Mandible**



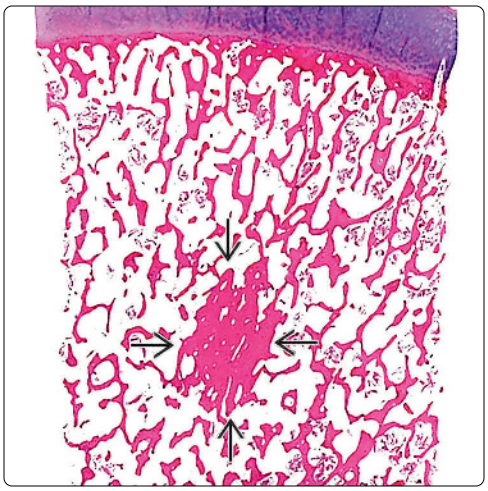
**Gross Photo of Bone Island Arising in Rib**



Gross Photograph

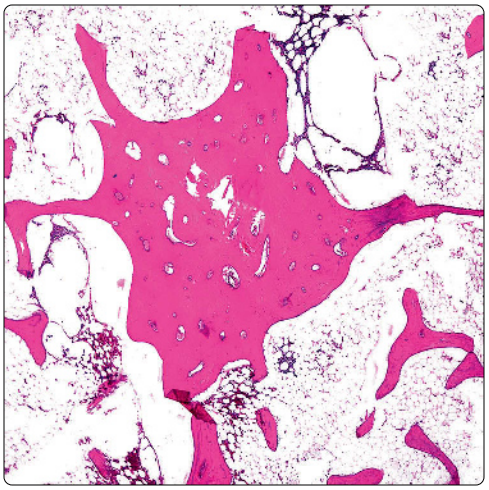


Whole-Mount Section

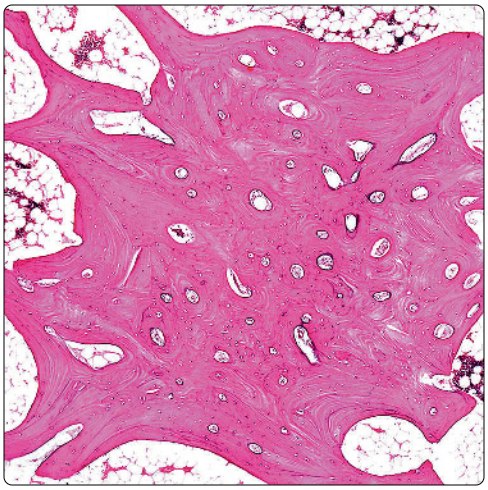


**(Left)** *Gross photograph shows an excised femoral head with an incidental bone island ⇨. The tumor is located beneath the articular cartilage and merges with the surrounding trabecular bone. The neighboring marrow is fatty and unremarkable.* **(Right)** *Low-power view shows a bone island involving the medullary cavity of the proximal femur ⇨. The lesion is composed of cortical-type bone that blends imperceptively with the surrounding trabecular bone.*

Light Microscopy

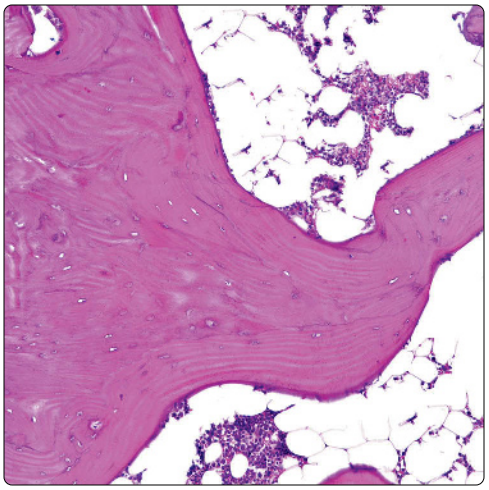


Light Microscopy

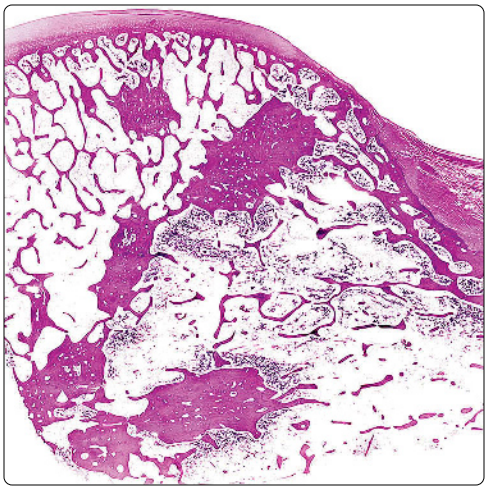


**(Left)** *Histologic section of a solitary bone island is shown. The bone island is composed of cortical-type bone with haversian-like canals and transitions into the adjacent cancellous bone. The surrounding marrow is predominately fatty with scattered islands of hematopoietic cells.* **(Right)** *Bone island with numerous haversian-like systems scattered throughout the lesion is shown. The bone of the tumor is sharply demarcated from the adjacent marrow.*

Periphery of Bone Island



Osteopoikilosis



**(Left)** *Close view of the transition between the periphery of the bone island is shown as it merges with an adjacent bone trabeculum. The bone is woven and lamellar and has a sharp border with the surrounding fatty and hematopoietic marrow.* **(Right)** *Resected femoral head from a patient with osteopoikilosis shows that numerous bone islands are present within the medullary cavity. The lesions are round to oval and vary in size. The margins are irregular and spiculated.*

# Osteoma

KEY FACTS

## TERMINOLOGY

- Benign surface bone-forming tumor, usually composed of cortical-type bone

## CLINICAL ISSUES

- Usually small and solitary
- Commonly asymptomatic and incidental finding
- Most frequently develop in craniofacial skeleton
- Appendicular tumors are very uncommon
- Multiple lesions raise possibility of Gardner syndrome
- Asymptomatic lesions can be observed
- Symptomatic lesions can be conservatively excised

## IMAGING

- Small and uniformly radiodense
- Sharply marginated with well-formed periosteal reaction
- Oval to dome-shaped with broad attachment to cortical surface
- Underlying cortex is not involved

## MACROSCOPIC

- Generally < 2 cm in diameter; round, tan-white, and hard
- Resembles cortical bone with which it merges

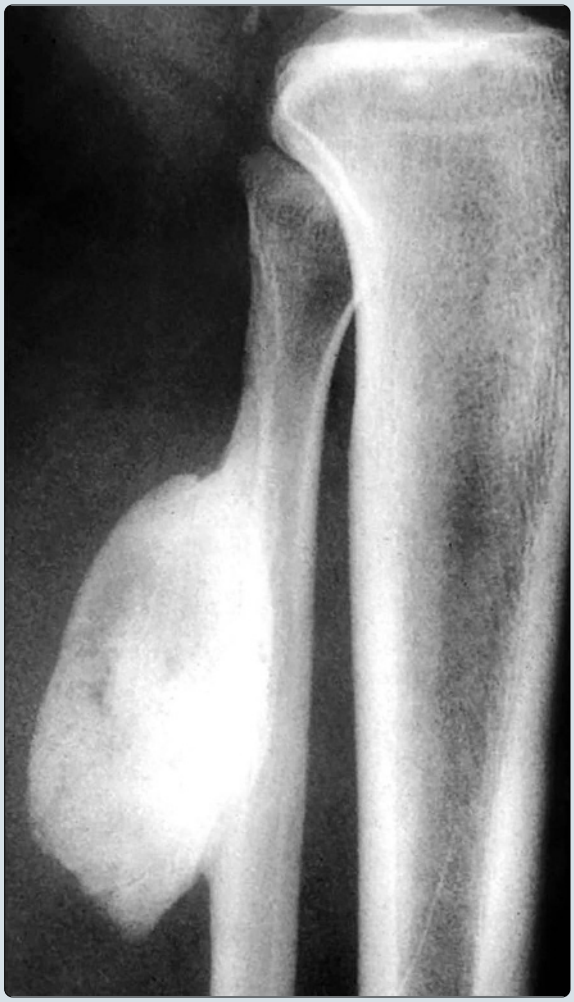
## MICROSCOPIC

- Consists mainly of lamellar bone admixed with some woven bone
- Bone has cortical-type architecture
- Minority of osteomas composed of trabecular bone
- Lesional osteoblasts and osteocytes usually inconspicuous

## DIAGNOSTIC CHECKLIST

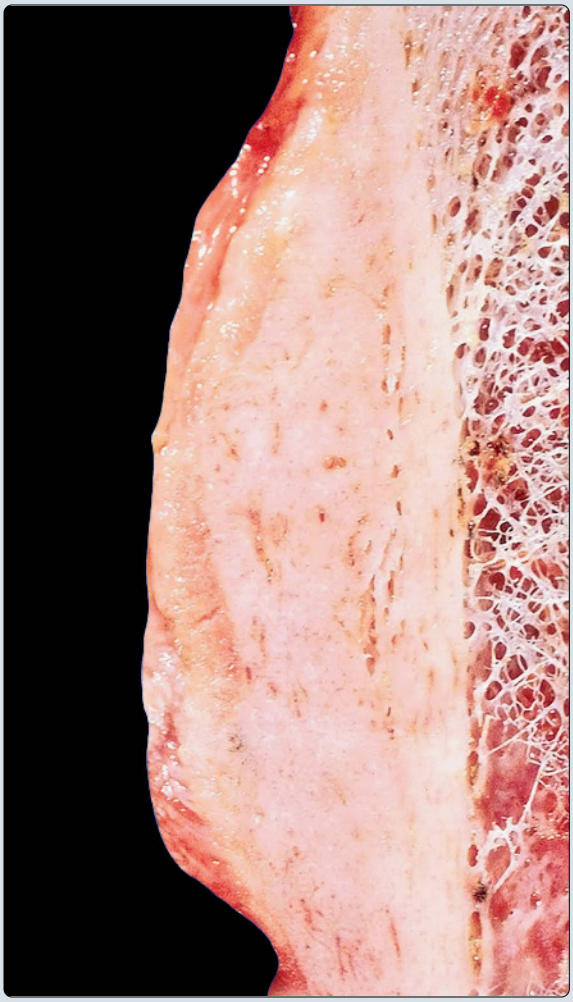
- Well-formed cortical bone and banal cytology distinguishes osteoma from osteosarcoma
- Intact cortex and absence of cartilage excludes osteochondroma
- Hypocellularity of lesion is evidence against myositis ossificans
- Melorheostosis and osteoma are histologically similar

**Osteoma of Fibula**



*Radiograph of proximal lower leg shows a dense, well-defined ossific mass on the surface of the proximal fibula. There is thick, periosteal bone apposition proximal to the mass that is triangular in shape.*

**Osteoma of Long Bone Resection Specimen**



*Osteoma is composed of hard, dense, compact bone with a broad attachment to the underlying cortex. A triangular-shaped zone of subperiosteal bone is present proximal and distal to the osteoma.*

## TERMINOLOGY

### Abbreviations

- Osteoma (OS)

### Synonyms

- Torus palatinus (palate) and mandibularis (mandible)

### Definitions

- Benign surface tumor composed of cortical-type bone
  - Minority composed of trabecular bone (trabecular osteoma)

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Paranasal sinus osteoma: 3-4%
  - Cranial osteoma at autopsy: 4-5%
  - Accounts for 0.03% of biopsied primary bone tumors
- Age
  - Most common in 4th to 6th decades of life
- Sex
  - No predilection

### Site

- Craniofacial skeleton most common
  - Often located in frontal and ethmoid sinuses (75%)
  - Sphenoid sinus, cranium, jaw
- Appendicular skeleton rare
  - Long tubular bones
    - Femur and tibia most common

### Presentation

- Slow-growing small lesions; usually incidental finding
- Large lesions: Symptoms related to anatomic location
  - Sinus tumors: Obstruction and mucocele
  - Orbital tumors: Exophthalmos and vision disturbances
  - Oral tumors: Interfere with dentures and mastication
  - Appendicular tumors: Palpable hard mass
- Usually solitary
  - Multiple tumors may be seen in Gardner syndrome

### Treatment

- Observation
- Simple excision

### Prognosis

- Excellent, no recurrence

## IMAGING

### General Features

- Uniformly radiodense surface lesion well demarcated from soft tissue
- Ovoid with broad base of attachment to cortex
- Dense periosteal reaction along margin of attachment may be present

### MR Findings

- Low signal intensity on T1- and T2-weighted images
  - Lesion does not enhance with contrast

### CT Findings

- Well-delineated surface mass with cortical density

### Bone Scan

- May show increased or no radiotracer uptake

## MACROSCOPIC

### General Features

- Generally < 2 cm in diameter
- Oval, round, or hemispheric
- Hard
- Tan to white
- Resembles cortical bone with which it merges
- Well-formed, triangular-shaped subperiosteal reactive bone may surround attachment site to cortex

## MICROSCOPIC

### Histologic Features

- Admixture of lamellar and woven bone with haversian-like systems
- Infrequently composed of trabecular bone
- Growing lesion may have fibrous component mimicking fibroosseous tumor
- Osteoblasts rimming bone are inconspicuous and elongate
  - Growing lesions lined by plump metabolically active osteoblasts
    - Abundant eosinophilic cytoplasm and nuclei polarized away from bone-forming surface
- Inactive osteoblasts and osteocytes have small round dark nuclei and no nucleoli

## DIFFERENTIAL DIAGNOSIS

### Bone-Forming Lesions

- Parosteal osteosarcoma
  - Contains prominent spindle cell component
- Juxtacortical myositis ossificans
  - Composed of hypercellular cancellous bone
- Melorheostosis
  - Dripping candle wax configuration
- Osteochondroma
  - Has cartilage cap

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Well-formed cortical bone and banal cytology distinguishes osteoma from osteosarcoma
- Intact cortex and absence of cartilage excludes osteochondroma
- Hypocellularity is evidence against myositis ossificans
- Melorheostosis and osteoma are histologically similar

## SELECTED REFERENCES

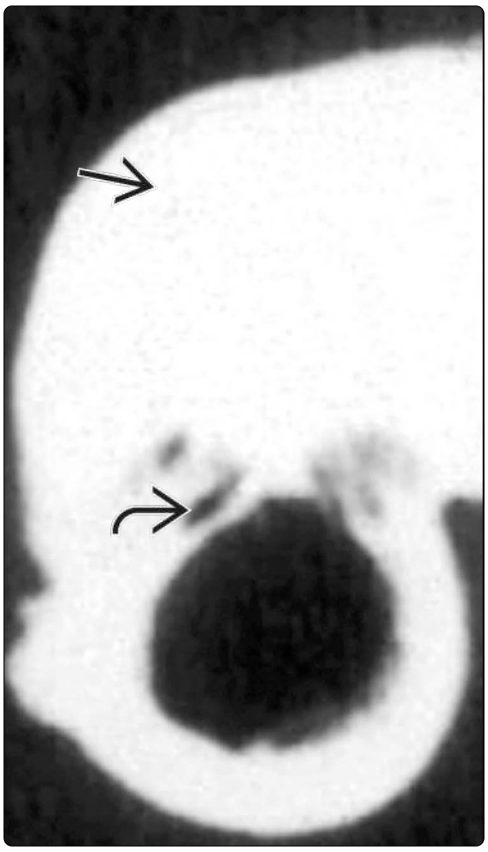

1. Halawi AM et al: Craniofacial osteoma: clinical presentation and patterns of growth. Am J Rhinol Allergy. 27(2):128-33, 2013
2. Greenspan A. Benign bone-forming lesions: osteoma et al: clinical, imaging, pathologic, and differential considerations. Skeletal Radiol. 22(7):485-500, 1993
3. O'Connell JX et al: Solitary osteoma of a long bone. A case report. J Bone Joint Surg Am. 75(12):1830-4, 1993

**Osteoma of Femur**

**Large Osteoma of Femur**

**(Left)** *Anteroposterior view of the left thigh shows a dense, well-defined ossific mass on the surface of the medial femur. There is periosteal bone apposition proximal and distal to the attachment site ➡.* **(Right)** *CT shows a well-defined, homogeneously sclerotic mass ⇨ contiguous with the outer cortex of the femur and extending into the soft tissues. The underlying cortex contains cylindrical lucencies ⇨, which contain feeding blood vessels that branch into the tumor.*



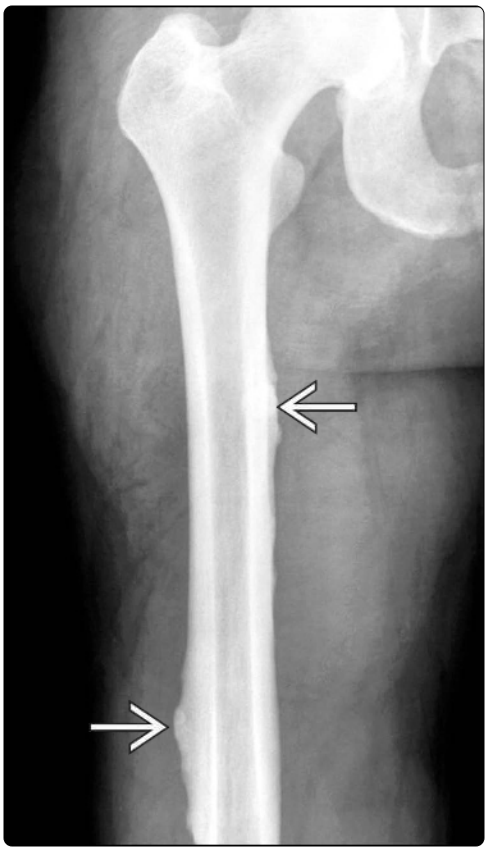


**Osteoma Resembling Cortical Bone**

**Osteomas in Gardner Syndrome**

**(Left)** *Gross photograph shows osteoma of femur cut in a sagittal plane. The mass merges imperceptibly with the underlying cortex. Notice how the proximal and distal portions of the cortex adjacent to the mass are thickened by reactive, well-formed bone both proximally and distally ➡.* **(Right)** *AP radiograph of femur in a patient with Gardner syndrome shows 2 elongated sessile osteomas. The masses protrude from the medial and lateral surfaces of the cortex ➡ and merge with the underlying bone.*

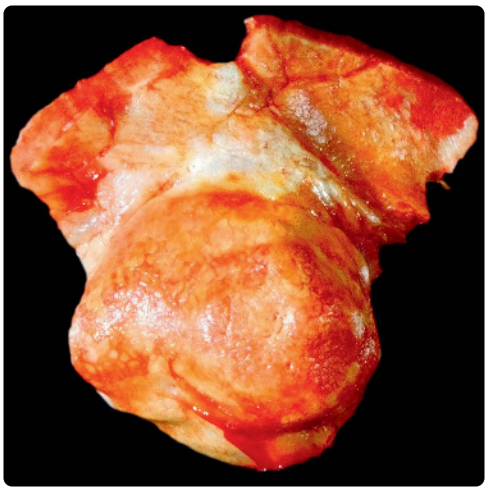




### Osteoma Displacing Eye



### Marble-Like Mass



**(Left)** *CT shows a well-defined, oval, homogeneously sclerotic osteoma. The tumor is contiguous with the outer cortex of the orbital roof, extends into the periorbital soft tissues, and displaces the globe inferiorly. The underlying cortex is intact.* **(Right)** *Gross photograph of resected osteoma shows a marble-like mass that protrudes from the cortex. The tumor is covered by a translucent layer of periosteum and is tan-white, hard, and well circumscribed.*

### Osteoma of Sinus Producing Mucocele

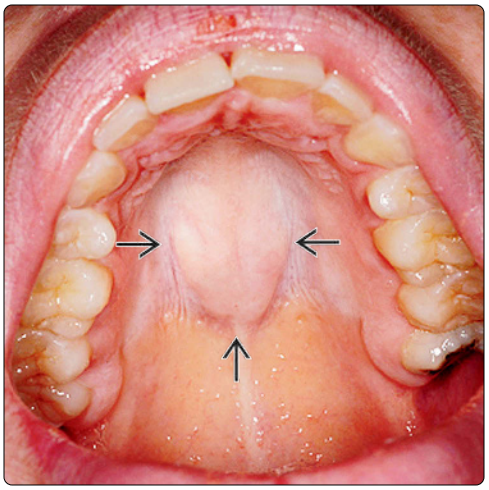


### MR of Mucocele Caused by Osteoma



**(Left)** *Axial CT shows a homogeneously dense osteoma projecting into the frontal lobe from the inner table of the skull. Note the low-density area representing a mucocele ➔ surrounding the lesion adjacent to the frontal lobe of the brain.* **(Right)** *T2-weighted MR shows a heterogeneous, mostly hypointense mass projecting from the inner table of the skull. There is a lobulated, hyperintense mucocele ➔ adjacent to the lesion. The mucocele distorts the adjacent brain parenchyma.*

### Osteoma of Palate

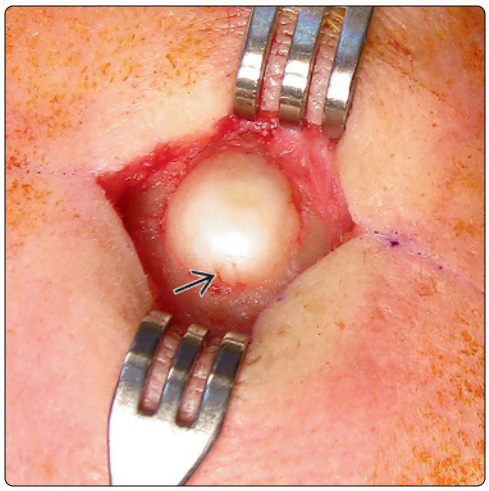


### Osteomas in Gardner Syndrome

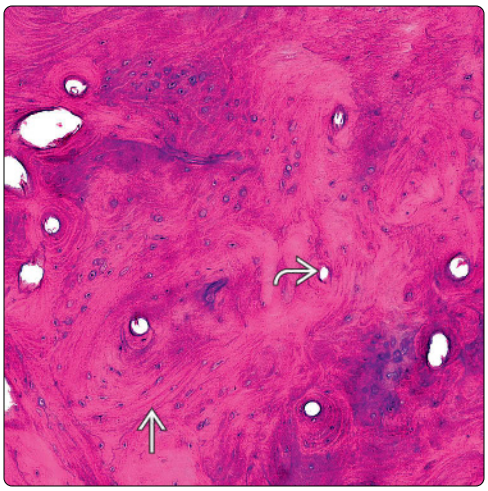


**(Left)** *In this clinical photograph of torus palatinus, the mass appears as a midline, oval, tan-white lesion ➔ beneath the oral mucosa lining. The mucosa is intact and translucent. (Courtesy T. Dodson, MD.)* **(Right)** *AP radiograph shows gnathic bones in a patient with confirmed Gardner syndrome. Multiple large, lobulated osteomas arise from the surface of the mandible bilaterally ➔. The radiodense masses are well circumscribed from the surrounding soft tissues.*

**Osteoma at Surgery**

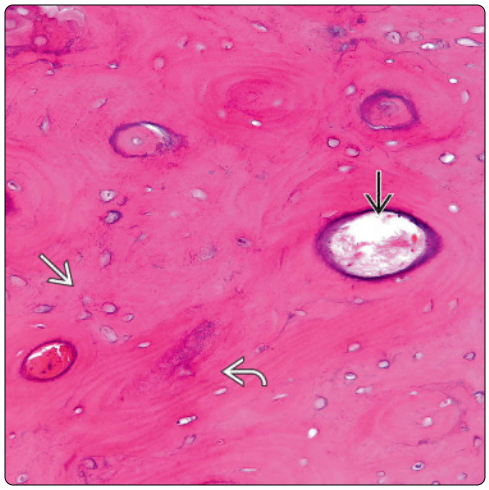


**Osteoma Having Cortical-Like Features**

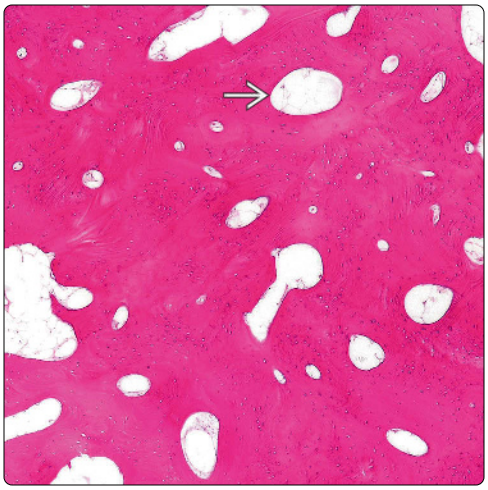


**(Left)** *Surgical exposure of an osteoma of the forehead shows that the small round lesion is pearly white. The tumor easily separates and is sharply demarcated from the neighboring soft tissues. The vascularized periosteum ⇨ can be seen covering a portion of the periphery of the lesion.* **(Right)** *Hematoxylin & eosin section of osteoma shows that the tumor has cortical-like architecture. The bone is composed of an admixture of woven and lamellar bone ➡. Note the haversian-like canals that are scattered throughout the mass ➡.*

**Woven and Lamellar Bone**

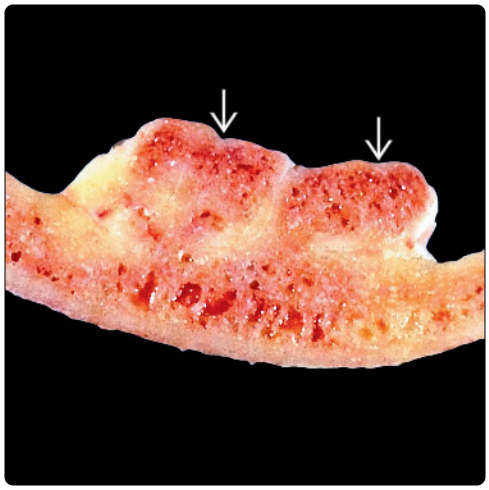


**Osteoma With Haversian-Like Canals**



**(Left)** *Hematoxylin & eosin section of osteoma shows that the bone is both woven ➡ and lamellar ➡ in pattern. The osteoblasts lining the surface of the haversian-like canal are not well seen ⇨, and the osteocytes in the matrix are small and randomly distributed.* **(Right)** *Hematoxylin & eosin of osteoma shows haversian-like canals ➡ that are prominent and vary in size and shape. The lining osteoblasts are small and osteocytes are numerous. Some of the spaces are filled with fatty marrow.*

**Multinodular Mass on Calvarium**

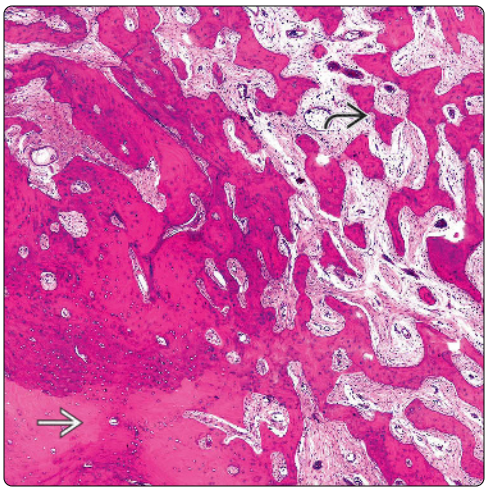


**Trabecular Osteoma**

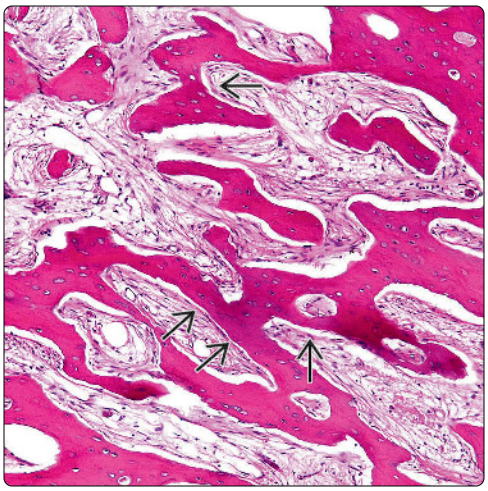


**(Left)** *Gross photograph shows cancellous osteoma arising from the inner table of the skull. The bilobed tumor ➡ has a spongy appearance with the intertrabecular spaces filled with marrow.* **(Right)** *Cancellous osteoma of the skull merges with the underlying inner table. The surface of the lesion is composed of a thin plate of cortical-type bone, and the central component consists of interconnecting trabeculae of mainly lamellar bone.*

### Mixture of Cortical and Cancellous Bone

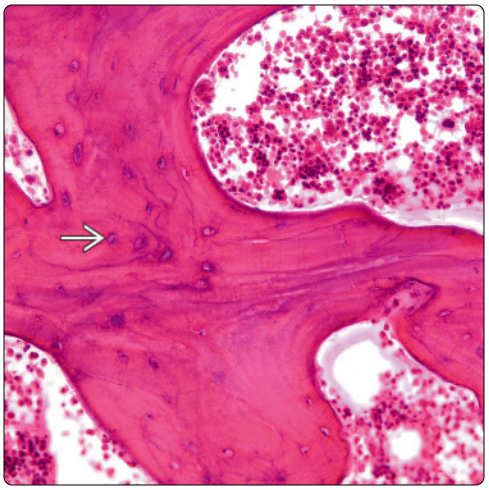


### Osteoma Composed of Trabecular Bone

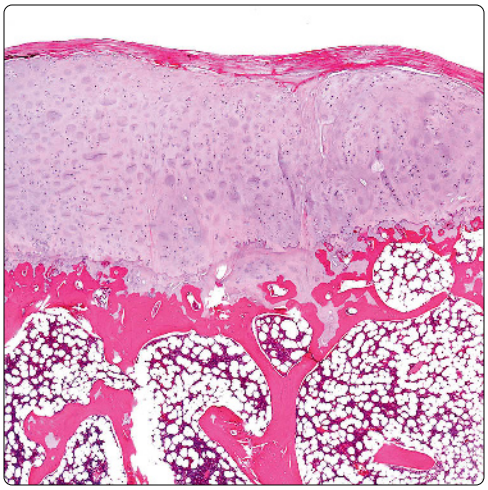


**(Left)** *Hematoxylin & eosin section shows osteoma with cortical and cancellous patterns. The intertrabecular spaces are filled with loose connective tissue, which contains dilated feeder blood vessels.* **(Right)** *Hematoxylin & eosin section of cancellous osteoma shows that the interconnecting trabeculae are covered by prominent osteoblasts. The bone is surrounded by loose connective tissue.*

### Trabeculae Surrounded by Marrow

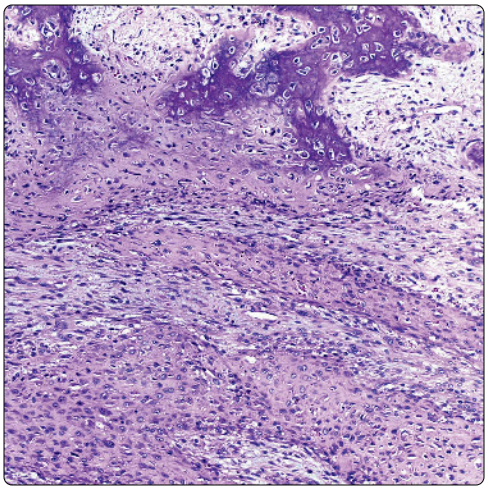


### Cap of Osteochondroma

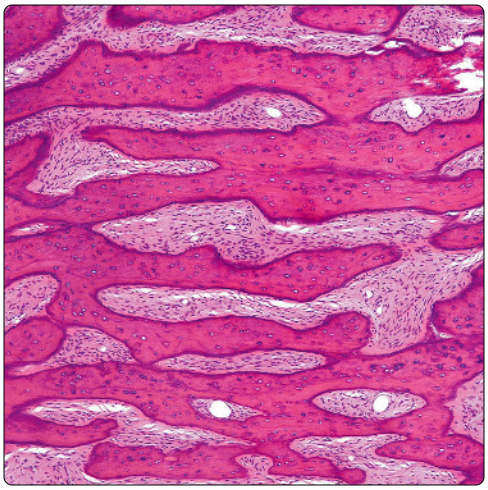


**(Left)** *Interconnecting trabeculae in osteoma are composed of collagen fibers that are arranged in a lamellar pattern. The surface osteoblasts are inconspicuous. The osteocytes are small. The marrow spaces are filled with hematopoietic elements.* **(Right)** *Osteochondroma has a cap of hyaline cartilage that resembles disorganized growth plate cartilage. This feature and the continuity of the center of the tumor with the underlying medullary cavity of the originating bone distinguishes osteochondroma from osteoma.*

### Myositis Ossificans



### Parosteal Osteosarcoma



**(Left)** *Myositis ossificans is hypercellular with primitive-appearing trabecular woven bone that merges with more mature-appearing bone peripherally. The appearance of the bone and hypercellularity helps distinguish it from osteoma.* **(Right)** *Parosteal osteosarcoma is composed of long trabeculae of woven bone surrounded by fascicles of spindle cells. The architecture of the bone and spindle cells distinguish the tumor from osteoma.*

# Osteoid Osteoma

KEY FACTS

## TERMINOLOGY

- Benign bone-forming tumor characterized by its small size, limited growth potential, classic pattern of pain, and composition of woven bone trabeculae rimmed by osteoblasts

## CLINICAL ISSUES

- Accounts for ~ 13% of all primary benign bone tumors and 3% of all other primary bone tumors
- Peak incidence: 5-25 years (76%)
- Located in long tubular bones, especially lower extremity, followed by posterior elements of spine and tubular bones of hands and feet
- Presents as severe localized pain that is often worse at night, which is relieved by aspirin or related medications
- Induces joint pain that may mimic primary articular disorder
- Most common cause of painful scoliosis
- Treatment of choice is radiofrequency ablation with surgical removal in select patients
- Excellent prognosis as lesion is not locally aggressive and does not metastasize

## IMAGING

- Does not exceed 1-2 cm in diameter
- Lesion has well-defined margins and is round, lucent, and often contains variable amount of patchy central mineralization
- Nidus is surrounded by zone of subperiosteal or medullary sclerosis
- Increased uptake on bone scan

## ANCILLARY TESTS

- S100 and neurofilament show nerve fibers within and adjacent to tumor

## TOP DIFFERENTIAL DIAGNOSES

- Osteoblastoma
- Intraosseous abscess (Brodie abscess)
- Stress fracture

**Oval Radiolucency**



*AP plain radiograph of the distal femur shows an osteoid osteoma on the surface of the medial metaphyseal cortex. The oval tumor (nidus) manifests a small lucency with subtle central mineralization surrounded by a very thick layer of periosteal new bone formation.*

**Red-White Tumor**



*Osteoid osteoma appears as a well-circumscribed, oval, hemorrhagic, red, solid mass. The tumor is surrounded by a thick rind of reactive bone.*

## TERMINOLOGY

### Abbreviations

- Osteoid osteoma (OO)

### Definitions

- Benign bone-forming tumor characterized by small size, limited growth potential, classic pattern of pain, and composition of woven bone trabeculae rimmed by osteoblasts

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Accounts for 13% of benign bone tumors
- Age
  - Usually develops in adolescents and young adults
    - Peak incidence: 5-25 years (76%)
- Sex
  - M:F = 2-3:1

### Site

- Long tubular bones (75% of cases)
  - Proximal femur is most common location
  - Diaphysis and metaphysis (65-80%), infrequently epiphysis
  - Subperiosteal and intracortical (70-80%), intramedullary (25%); intraarticular is uncommon
- Vertebral column (10-14% of cases)
  - Posterior elements (90%), body (10%)
- Short tubular bones of hands and feet (8-10%)

### Presentation

- Severe localized pain worse at night, relieved by aspirin or nonsteroidal antiinflammatory medications
  - High levels of prostaglandin E2 and prostacyclins
  - COX-2 overexpression by osteoblasts
- Joint pain and effusion can mimic articular disorder
- Swelling can simulate infection with tumors in phalanges
- Painful scoliosis due to spasm of paravertebral muscles
  - Most common cause of painful scoliosis
- Overgrowth of bone when located near growth plate
- Limp and limitation of range of motion

### Treatment

- Radiofrequency ablation
  - No removal of normal tissue and outpatient procedure
- Curettage, burring, cryoablation, ultrasound therapy, resection
- Medical therapy and observation in select patients

### Prognosis

- Excellent; local recurrence rate 0-10%

## IMAGING

### General Features

- Lytic tumor (nidus) is 1-2 cm in diameter
- Well-defined margins and central patchy mineralization
- Surrounded by reactive sclerosis and edema
  - Extensive reactive changes simulate aggressive neoplasm, obscures lesion
- Usually solitary and rarely multifocal

### Radiographic Findings

- Round, radiolucent with central mineralization
- Peripheral sclerosis frequent and may be extensive

### MR Findings

- Isodense to skeletal muscle on T1-weighted images
- Lucent components and surrounding edema have increased signal intensity on T2-weighted images

### CT Findings

- Well-demarcated, small, round with central mineralization, bordered by reactive bone

### Bone Scan

- Marked uptake of radionuclide

## MACROSCOPIC

### General Features

- Round, well demarcated, gritty, dark red with central tan-white speckles and < 2 cm
- Surrounded by dense sclerotic bone

## MICROSCOPIC

### Histologic Features

- Haphazard, interanastomosing trabeculae of woven bone rimmed by osteoblasts
  - Neoplastic bone may be sheet-like or solid
  - Some osteoblasts may be epithelioid
  - Cartilaginous foci are rare
- Scattered osteoclasts often on surfaces of trabeculae
- Vascular stroma containing loose connective tissue

## ANCILLARY TESTS

### Immunohistochemistry

- S100 and neurofilament show nerve fibers involving tumor

### Genetic Testing

- Monosomies and chromosome 22q abnormalities

### Hormone Production

- Produces osteocalcin, which can raise blood glucose

## DIFFERENTIAL DIAGNOSIS

### Osteoblastoma

- > 2 cm; morphologic overlap

### Intraosseous Abscess (Brodie Abscess)

- Rich in inflammatory cells and granulation tissue

### Stress Fracture

- Reactive woven bone network well oriented (not haphazard) around fractured trabeculae

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2. Boscainos PJ et al: Osteoid osteoma. Orthopedics. 36(10):792-800, 2013
3. Trotta B et al: Benign osteoid-producing bone lesions: update on imaging and treatment. Semin Musculoskelet Radiol. 17(2):116-22, 2013

**Cortical Thickening**



**Marked Edema**

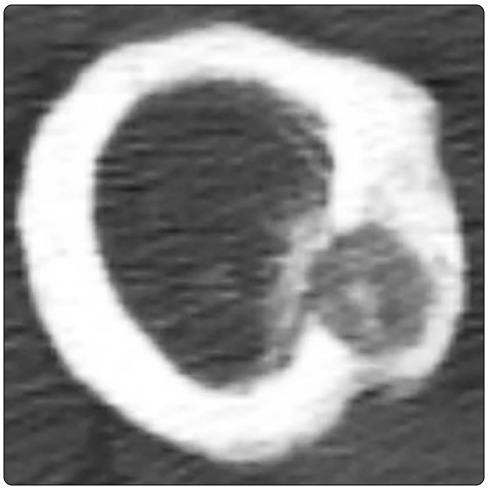


**(Left)** *A child presents with leg pain that is worse at night, and a radiograph shows a region of cortical thickening ⇨. Within the area of sclerosis is a subtle oval lucency that represents an osteoid osteoma ⇨.* **(Right)** *Coronal T2-weighted MR of the right hip shows an osteoid osteoma ⇨ on the surface of the bone. The tumor is partially obscured by extensive intramedullary, periosteal, and soft tissue edema ⇨ (bright white areas).*

**Oval Lucency With Surrounding Sclerosis**



**Round Intracortical Tumor**



**(Left)** *Osteoid osteoma is oval, radiolucent, and often has a mineralized central portion ⇨. This tumor involves the cortex and has elicited abundant subperiosteal well-formed reactive bone that is sclerotic ➡.* **(Right)** *In this axial CT, the osteoid osteoma is intracortical and has elicited reactive new bone within the medullary cavity beneath the periosteum. The tumor is round and lytic with a small central mineralized region.*

**Eccentric Tumor**



**Intracortical Tumor**



**(Left)** *This radiograph shows an osteoid osteoma of the distal ulnar metaphysis. The oval, well-demarcated, lytic tumor ➡ eccentrically involves the cortex and is surrounded by reactive new bone ⇨.* **(Right)** *This axial CT exhibits the features characteristic of osteoid osteoma. The tumor is small, round, and lytic ➡ with central mineralization and is surrounded by abundant subperiosteal reactive bone ⇨.*

**Osteoid Osteoma of Posterior Elements**



**Intense Uptake**



**(Left)** *AP radiograph of the cervical spine demonstrates a round osteoid osteoma ➡ of the left posterior elements of C7. The lesion is mostly lytic, although a small amount of central hazy mineralization is visible.* **(Right)** *Radionuclide bone scan (posterior view) shows a small focus of intense uptake ➡ in the left posterior elements of C7, representing the osteoid osteoma. A larger, but much less intense, "halo" of uptake surrounds the lesion representing reactive tissue changes.*

**Tumor in Base of Pedicle**



**Surrounding Edema**

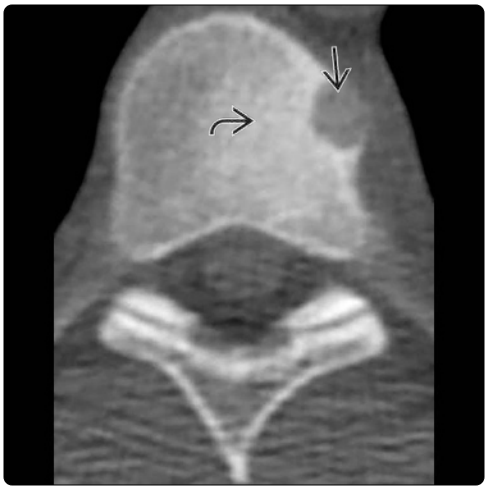


**(Left)** *Osteoid osteoma often develops in the posterior elements of the spine. In this case, the oblong lytic tumor is well circumscribed ➡ and involves the base of the pedicle.* **(Right)** *Osteoid osteoma often produces edema of the surrounding tissues. In this axial T2-weighted fat-saturated image a rim of bright intensity ➡ edematous tissue encircles the tumor ➡.*

**Round Tumor in Posterior Elements**



**Osteoid Osteoma of Vertebral Body**

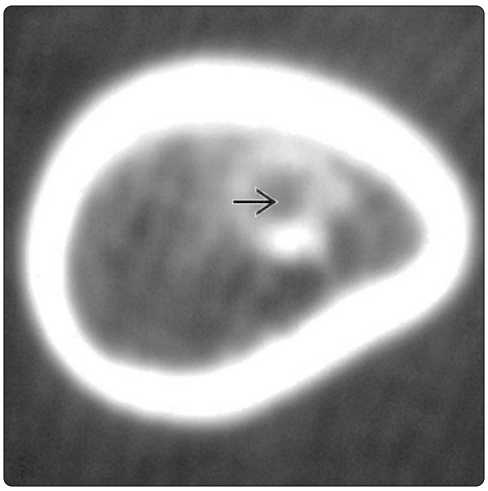


**(Left)** *Sagittal reformation of a CT scan demonstrates an osteoid osteoma of the posterior elements of T12. The lesion is 1 cm in diameter ➡, contains ring-like internal mineralization, and is surrounded by dense sclerosis ➡ of the pedicle and articular facets.* **(Right)** *It is uncommon for osteoid osteoma to be centered in the vertebral body. In this axial reformatted CT, the eccentric lytic tumor ➡ is surrounded by a rim of sclerosis ➡.*

### Marked Sclerosis

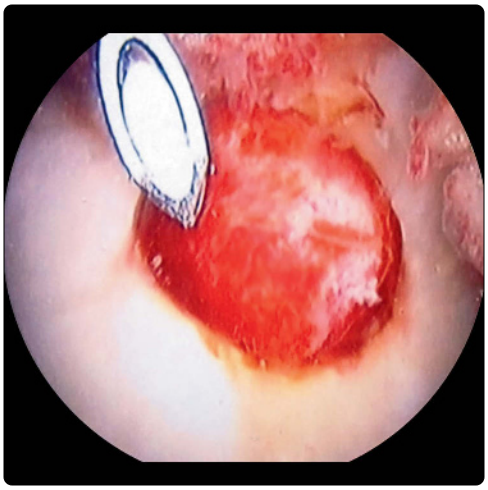


### Intramedullary Tumor

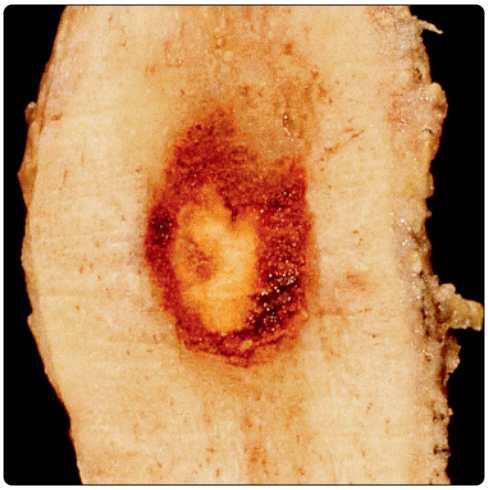


**(Left)** *Axial CT of the ilium shows an osteoid osteoma within the cancellous bone. It is surrounded by very dense sclerosis, which merges with the endosteum of the cortex. Little or no periosteal reaction is present.* **(Right)** *Axial CT of the distal femur shows a purely intramedullary lytic osteoid osteoma. This location is relatively uncommon, and when it occurs, periosteal reaction may be minimal. Note the irregular rim of surrounding sclerosis.*

### Arthroscopic View of Tumor

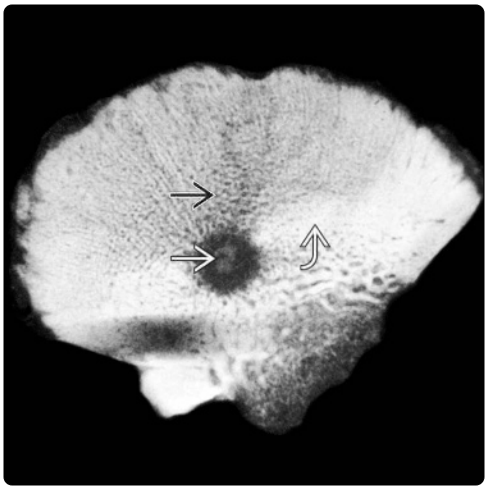


### Red-White, Well-Demarcated Mass

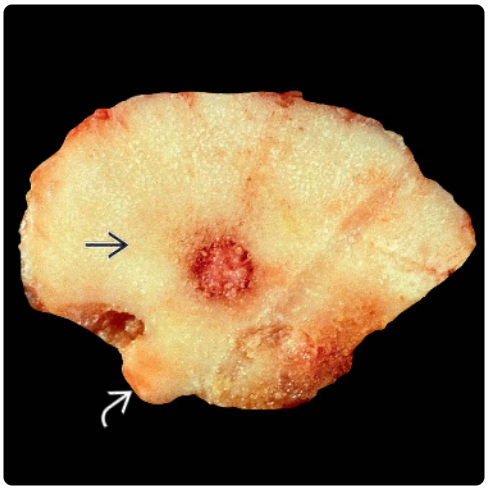


**(Left)** *Arthroscopic view of osteoid osteoma shows the round, bulging, red tumor. The white tissue surrounding the mass is smooth articular cartilage.* **(Right)** *Gross photograph of a resected osteoid osteoma of the fibula shows that the oval, red, intramedullary tumor has a central tan-white mineralized region. The adjacent cortex on one side of the mass is thickened by subperiosteal reactive new bone. The periosteum is intact.*

### Specimen Radiograph of Osteoid Osteoma

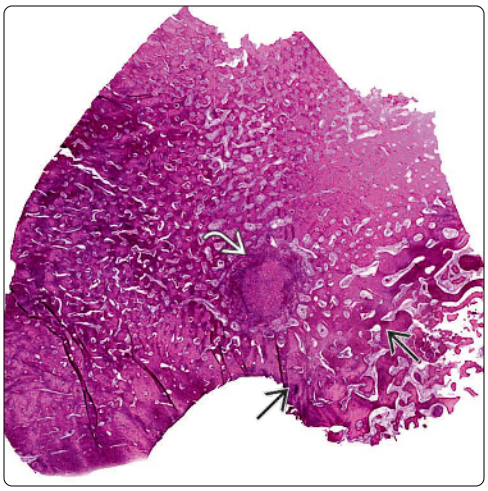


### Round Tumor Straddling Cortex

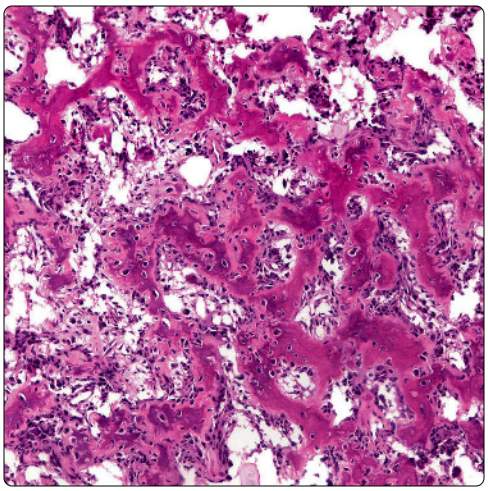


**(Left)** *Specimen radiograph of intracortical osteoid osteoma reveals the small, round, lucent tumor has a central area of mineralization and is sharply demarcated from the surrounding reactive bone. The involved portion of cortex has been trabecularized.* **(Right)** *Cross section of intracortical osteoid osteoma of long bone reveals the round, red-white nidus. The lesion has scattered white areas and is sharply demarcated from the peripheral reactive bone. A portion of the cortex is uninvolved.*

### Osteoid Osteoma With Sharp Margins

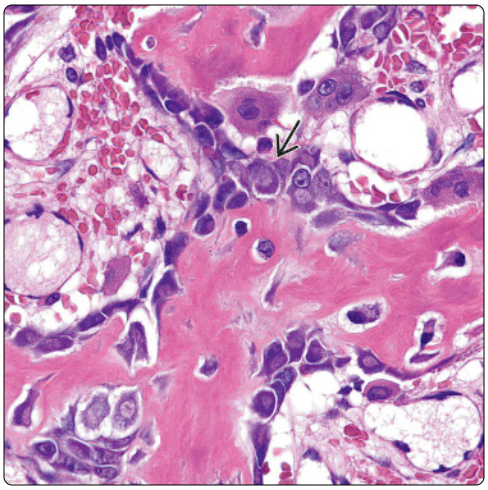


### Haphazardly Interconnecting Trabeculae

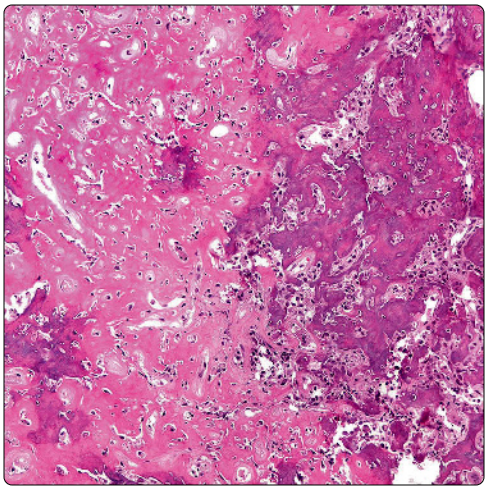


**(Left)** *Low-power image of a resected osteoid osteoma shows a small, round nidus located adjacent to the surface of the cortex. The lesion is surrounded peripherally by abundant reactive bone.* **(Right)** *Trabeculae of osteoid osteoma are randomly arranged and interconnect haphazardly. Large osteoblasts rim the woven bone surfaces, and intertrabecular spaces contain loose fibrovascular tissue.*

### Osteoblastic Rimming

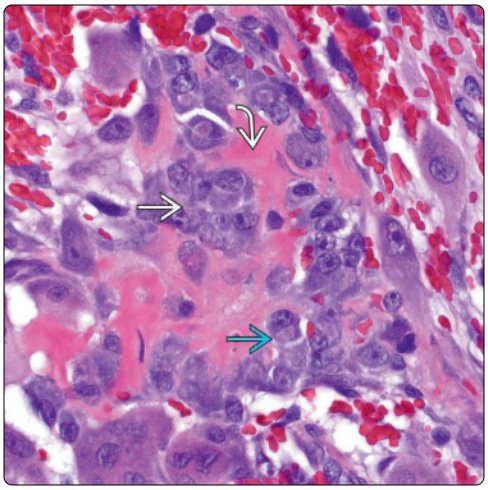


### Osteoid Osteoma With Sheet-Like Bone

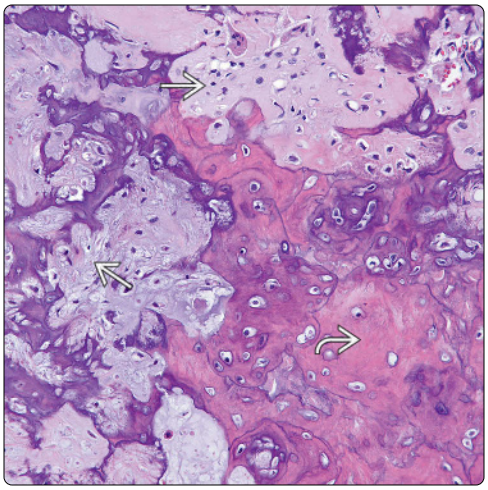


**(Left)** *Large osteoblasts rim the surface of the bone in osteoid osteoma. The intertrabecular spaces are filled with very vascular loose connective tissue.* **(Right)** *Osteoid osteoma composed of sheet-like bone matrix entraps bone-forming cells. The matrix varies in color from pink to purple, depending on its state of mineralization. The neoplastic matrix does not encase preexisting bony trabeculae.*

### Plump Osteoblasts



### Cartilage in Osteoid Osteoma



**(Left)** *Plumb osteoblasts rim the woven bone in this osteoid osteoma. Some of the osteoblasts have a perinuclear huff that represents a prominent Golgi apparatus.* **(Right)** *Some osteoid osteomas rarely have cartilage as a part of the matrix. In this example the basophilic cartilage is focally mineralized and is adjacent to the eosinophilic woven bone of the tumor.*

# Osteoblastoma

KEY FACTS

## CLINICAL ISSUES

- Benign bone-forming neoplasm > 2 cm in dimension
- Diagnosed in young adults with male predominance of 2:1
- Commonly arises in tubular bones and posterior elements of spinal column
- Presents with pain and swelling with neurologic symptoms in some spinal lesions
- Treated by curettage or en bloc excision
- Excellent prognosis with local recurrence rate of 20%

## IMAGING

- Expansile, well-defined mixed lytic and blastic mass with sclerotic margins

## MACROSCOPIC

- Well-circumscribed, gritty, tan-white, dark red mass
- Usually 2-5 cm in size

## MICROSCOPIC

- Sharply demarcated from adjacent preexisting and reactive bone
- Composed of haphazardly interconnecting trabeculae or sheet-like aggregates of woven bone rimmed prominently by metabolically active osteoblasts
- Intertrabecular tissue consists of loose, richly vascular connective tissue
- Variants contain cartilage, epithelioid osteoblasts, degenerative nuclear changes, and aneurysmal bone cyst-like changes

## TOP DIFFERENTIAL DIAGNOSES

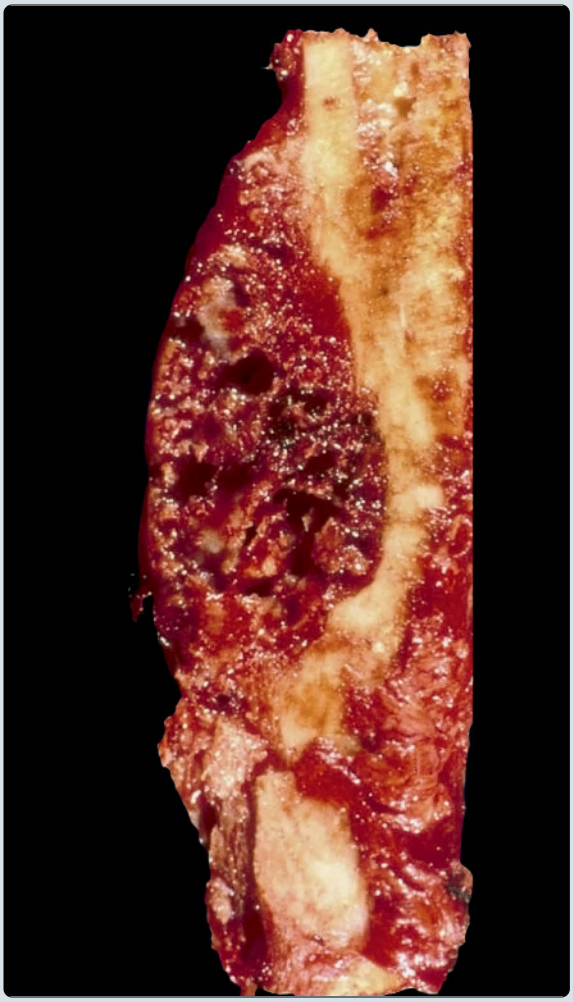
- Osteoid osteoma
- Aneurysmal bone cyst
- Osteoblastoma-like osteosarcoma

**Radiograph of Osteoblastoma**



*Radiograph of the humerus shows a lytic osteoblastoma of the mid shaft surrounded by solid periosteal new bone. It extends into periosseous soft tissues where cloud-like neoplastic ossification is noted.*

**Gross Photograph of Osteoblastoma**



*A long bone with an osteoblastoma involves the cortex and surface of bone. The well-circumscribed tumor is oval and red with speckled tan-white foci, which correspond to areas rich in neoplastic bone.*

## TERMINOLOGY

### Abbreviations

- Osteoblastoma (OB)

### Synonyms

- Giant osteoid osteoma

### Definitions

- Benign bone-forming neoplasm > 2 cm composed of woven bone trabeculae lined by osteoblasts

## ETIOLOGY/PATHOGENESIS

### Etiology

- Neoplasm: Some have deletion of portion of chromosome 22q12; does not upregulate miRNA-210

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Uncommon; accounts for 1% of primary bone tumors
- Age
  - Adolescents and young adults (2nd-4th decades)
    - 75% younger than 25 years old at diagnosis
- Sex
  - Males affected more frequently than females (2:1)

### Site

- Most commonly arise in tubular bones
  - ~ 60% develop in appendicular skeleton
    - Metadiaphyseal region of tubular bones
    - Cortical: 65%; medullary cavity: 35% of cases
    - Femur: 12%; tibia: 10%; bones of foot and ankle: 9%
- Axial skeleton frequently affected
  - 30% arise in spinal column
    - Posterior elements: Lamina, pedicles; vertebral body occurs secondarily
    - Cervical > lumbar > thoracic > sacral
- Craniofacial bones: 10% of cases; mandible most common

### Presentation

- Pain, swelling, decreased range of motion
- Spine tumors: Paresthesias, paraparesis, paraplegia
- Rarely associated with systemic "toxic" symptoms

### Treatment

- Curettage or selective en bloc resection

### Prognosis

- Curettage: Local recurrence in 20% of cases
- Aggressive variant behaves similar to conventional type
- Malignant transformation is exceptionally rare

## IMAGING

### Radiographic Findings

- Expansile, well-defined, oval mixed lytic and blastic mass
  - Peripheral lucent halo and central mineralization
  - Poorly defined margins in small minority
- Periosteal reactive bone; solid, laminated or spiculated

### MR Findings

- Well-delineated mass low to intermediate signal intensity on T1 and intermediate to high signal intensity on T2
  - Mineralized areas manifest as signal void (dark)
  - Tumor and edema enhance with contrast

### CT Findings

- Expansile lytic and sclerotic mass with circumscribed margins and surrounding reactive bone

### Bone Scan

- Intense uptake on scintigraphy

## MACROSCOPIC

### General Features

- Solitary, well circumscribed, tan-white, dark red, gritty
  - Rarely multifocal/multicentric
- Cystic changes prominent in 10% of cases
- Periosteal shell of reactive bone

### Size

- Range: 2-20 cm; most measure between 3-5 cm

## MICROSCOPIC

### Microscopic Features

- Sharply demarcated
- Trabeculae in haphazard, interconnecting, sheet-like patterns
  - Woven bone rimmed by plump osteoblasts and scattered osteoclasts
- Vascular connective tissue fills intertrabecular space
- Scattered mitoses with no atypical forms
- Necrosis usually absent or focal
- Occasional cystic change mimicking aneurysmal bone cyst
- 75% epithelioid osteoblasts: Aggressive OB
  - Large, polyhedral, abundant eosinophilic cytoplasm, vesicular nucleus, and prominent nucleolus
- Cartilaginous variant (5%) contains hyaline cartilage
- Pseudomalignant: Degenerative large, hyperchromatic, vacuolated nuclei

## DIFFERENTIAL DIAGNOSIS

### Osteoid Osteoma

- < 2 cm; characteristic clinical symptoms

### Aneurysmal Bone Cyst

- No haphazardly joining trabeculae of woven bone

### Osteoblastoma-Like Osteosarcoma

- Grows with infiltrative pattern

## DIAGNOSTIC CHECKLIST

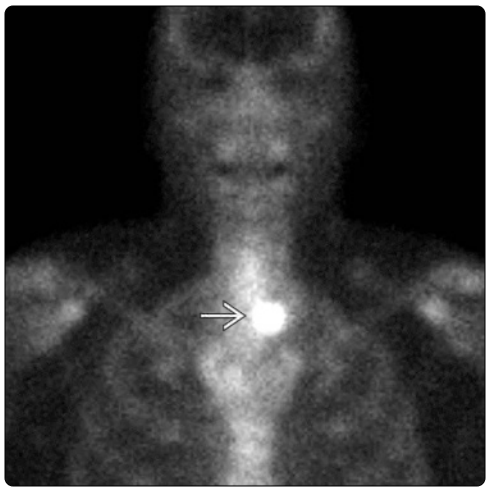
### Pathologic Interpretation Pearls

- Well demarcated: Neoplastic bone rimmed by osteoblasts

## SELECTED REFERENCES

1. Lucas DR et al: Osteoblastoma: clinicopathologic study of 306 cases. Hum Pathol. 25(2):117-34, 1994

**Avid Uptake on Bone Scan**

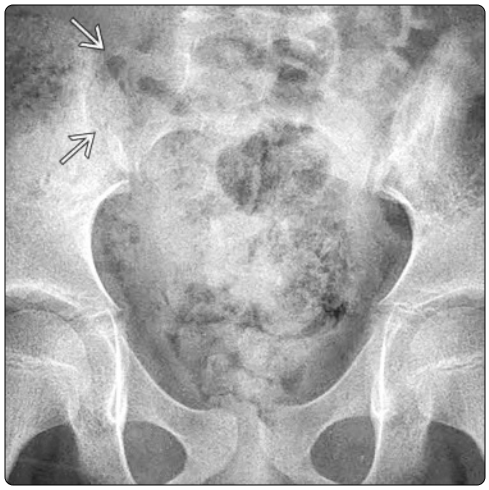


**Osteoblastoma Expanding Bone**

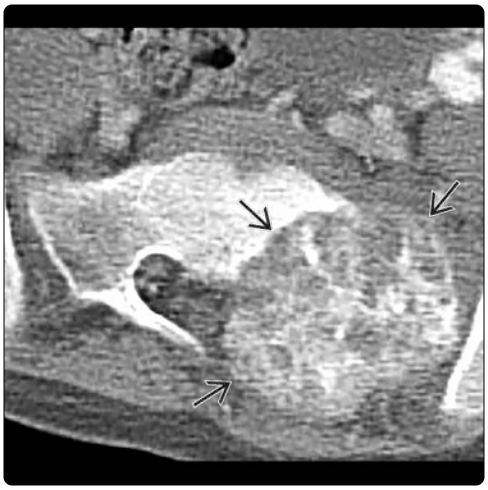


**(Left)** *AP bone scan shows a small oval focus of intense isotope uptake on the left of T2 ➡. (Right) CT scan through osteoblastoma of pedicle and lamina of the vertebra demonstrates a well-circumscribed, expansile, oval mass, which contains substantial internal fine ossification ⇨. The tumor impinges upon the spinal canal. Thick periosteal reaction is present along the surface of the lamina and the base of the spinous process ➡.*

**Subtle Tumor in Wing of Sacrum**



**Large Osteoblastoma of Sacrum**

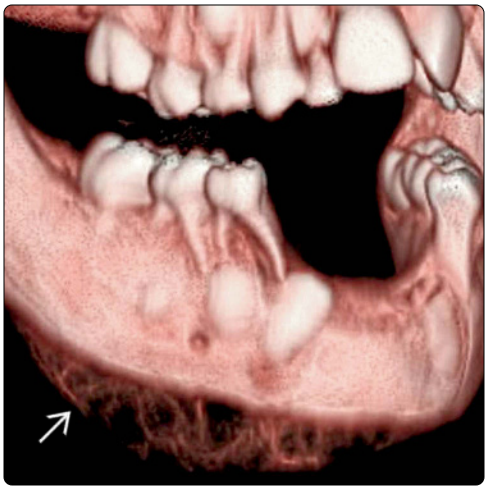


**(Left)** *The sacral wing contains a large osteoblastoma ➡ that is difficult to appreciate on the plan film. The tumor is mixed lytic and blastic and has a well-defined margin.* **(Right)** *This is the axial CT that corresponds to the accompanying plain film. The round tumor ⇨ is mixed lytic and blastic with a fine pattern of mineralization.*

**Osteoblastoma Expanding Mandible**



**Osteoblastoma of Mandible**



**(Left)** *Axial CT of a mandibular osteoblastoma shows a well-demarcated lytic lesion arising in the anterior symphyseal portion of the mandible. The tumor has faint internal ossifications and is surrounded by a shell of periosteal new bone formation ➡.* **(Right)** *A 3D reformation of a CT scan of an osteoblastoma of the mandible demonstrates a lytic lesion involving the inferior margin of the body, causing irregular elevation of the periosteum ➡. Several teeth were previously removed.*

Subperiosteal Osteoblastoma

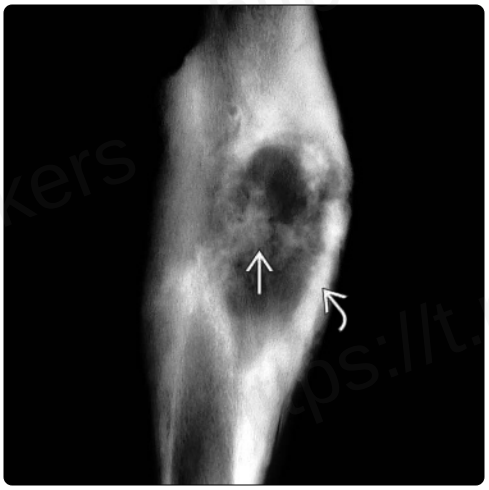


Subperiosteal Osteoblastoma

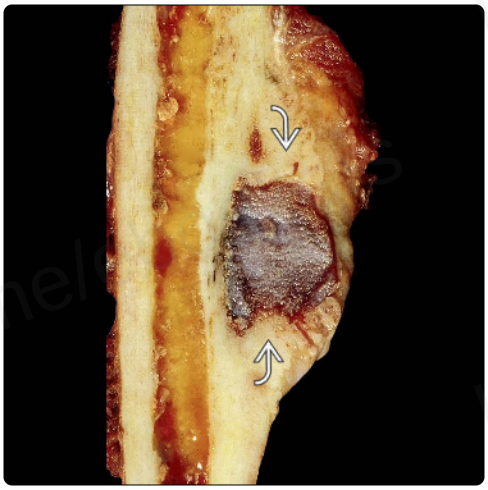


**(Left)** *Radiograph of the humerus shows a lytic osteoblastoma of the mid shaft surrounded by solid periosteal new bone. It extends into periosseous soft tissues where cloud-like neoplastic ossification is noted.* **(Right)** *Coronal T2-weighted MR demonstrates osteoblastoma of the outer surface of diaphyseal cortex surrounded by periosteal bone. No mineralization is detected.*

Osteoblastoma With Rim Reactive Bone



Red Oval Osteoblastoma

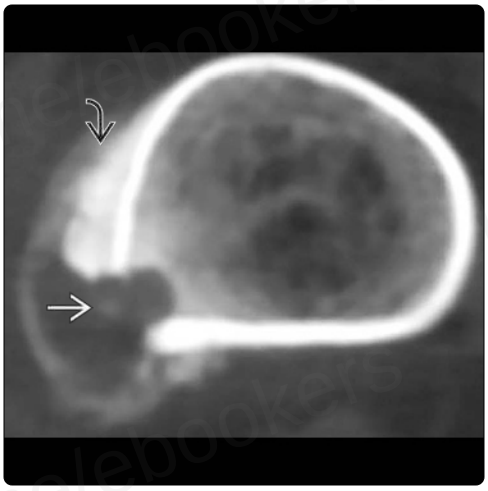


**(Left)** *Specimen radiograph demonstrates an oval lytic osteoblastoma arising in the cortex. Superior spatial resolution is possible because of the absence of overlying soft tissues. The tumor is well demarcated, contains faint mineralization, and is surrounded by well-formed reactive bone.* **(Right)** *A surface osteoblastoma is shown. The red-gray, sharply demarcated, solid tumor is surrounded by a thick rim of reactive periosteal new bone. The medullary cavity is filled with yellow fat.*

Abundant Reactive Woven Bone



Osteoblastoma Extending Through Cortex



**(Left)** *Osteoblastoma is eccentrically located in the distal femur. The tumor is oval, lytic, and well demarcated. There is abundant reactive bone that forms a zone of sclerosis around the tumor.* **(Right)** *Axial CT scan accompanying the radiograph shows a lytic tumor that contains a small area of central mineralization. The well-demarcated tumor is surrounded by a zone of sclerosis of varying radiodensity.*

### Large Osteoblastoma of Humerus



### Osteoblastoma Eroding Cortex



**(Left)** *AP radiograph demonstrates an unusually large and invasive osteoblastoma of the proximal humerus. The tumor is lytic with faint mineralization, involves the metadiaphysis, and extends into the surrounding soft tissues.* **(Right)** *T2-weighted MR shows a large osteoblastoma arising in the proximal humerus and extending into the adjacent soft tissue. The soft tissue mass engulfs a portion of the cortex. Low signal intensity areas correspond to foci of ossification.*

### Osteoblastoma With Sharp Margins



### Heterogeneous Osteoblastoma



**(Left)** *A large osteoblastoma spans the distal epiphysis, metaphysis, and diaphysis of the distal femur. The oval tumor is lytic with fine trabeculations. The tumor is well demarcated and has a sclerotic margin. The differential diagnosis includes giant cell tumor of bone.* **(Right)** *Coronal T2 fat-saturated weighted MR shows a large oval osteoblastoma of the distal femur. The tumor has a nodular architecture and is heterogeneous in intensity. The tumor is well circumscribed with mild surrounding edema.*

### Osteoblastoma Expanding Metatarsal



### Multifocal Osteoblastoma



**(Left)** *Plain radiograph of the foot demonstrates a large intramedullary, expansile osteoblastoma arising within the 4th metatarsal. The lesion exhibits faint ground-glass opacity of the sort more characteristic of fibrous dysplasia, indicating microscopic internal ossification.* **(Right)** *Sagittal T1-weighted MR through the lower leg and foot shows a rare example of multicentric osteoblastoma. Individual low and mixed signal intensity oval lesions are present in the anterior distal tibia and talus.*

### Large Cystic Osteoblastoma

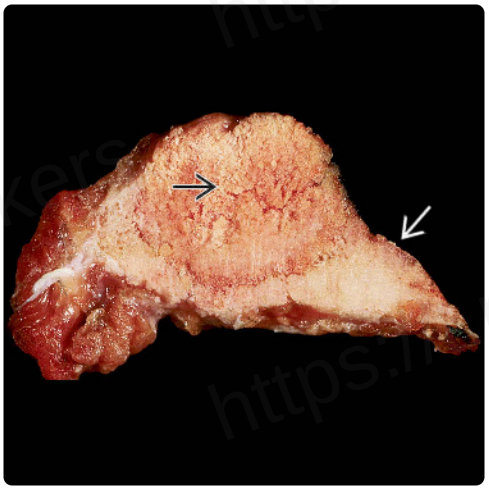


### Large Osteoblastoma With Hemorrhage

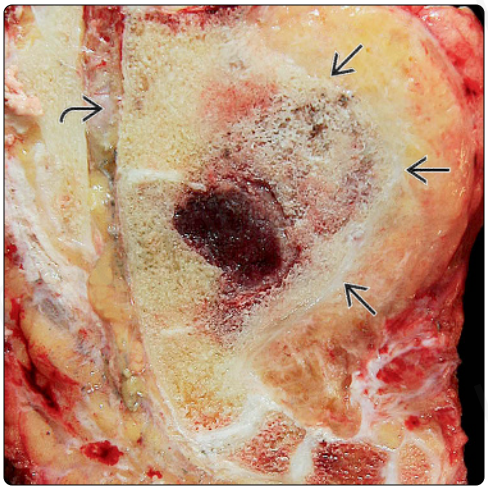


**(Left)** *Large round osteoblastoma from the spine is shown. The hemorrhagic tumor has undergone extensive cystic change causing it to mimic an aneurysmal bone cyst. Some of the cystic spaces are filled with clotted blood.* **(Right)** *A large, solid and cystic osteoblastoma arises in the proximal fibula in a growing child; note the growth plate ➡. The tumor involves the medullary cavity and extends through the cortex and into the soft tissues where it is covered by reactive bone ➡.*

### Osteoblastoma With Abundant Bone



### Osteoblastoma Expanding Bone



**(Left)** *An osteoblastoma of the scapula is shown. The oval, well-delineated tumor is solid tan-red and contains abundant neoplastic bone ⇨. The adjacent cortex is thickened by reactive bone ➡.* **(Right)** *A resected osteoblastoma is shown involving the distal sacrum. The tan hemorrhagic tumor involves 2 consecutive vertebral bodies crossing the intervertebral disc and protruding into the anterior soft tissues where it is surrounded by reactive bone ⇨. The spinal canal is visible ⇨.*

### Expansile Osteoblastoma of Rib

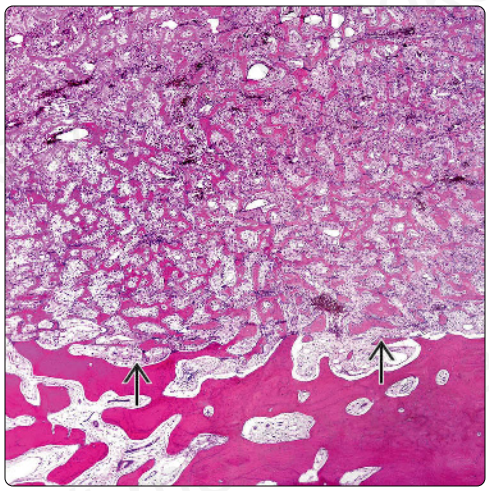


### Subperiosteal Tumor

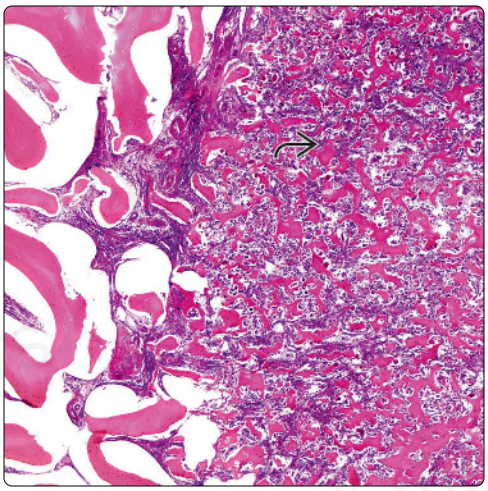


**(Left)** *Expansile osteoblastoma of the rib has well-circumscribed margins. The tumor is red-tan and the tan areas correspond to mineralized matrix.* **(Right)** *This osteoblastoma arises on the surface of a long bone. The tumor is tan-white, gritty, and contains scattered hemorrhagic cysts that are peripheral in location. The tumor is well defined from the adjacent cortex ⇨ and is covered by periosteum ➡.*

### Sharply Demarcated Osteoblastoma

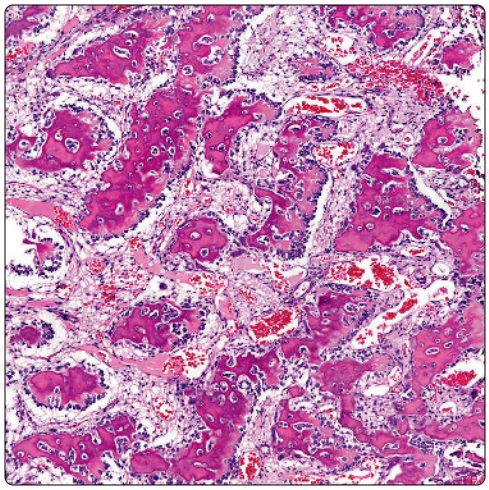


### Sharp Margin

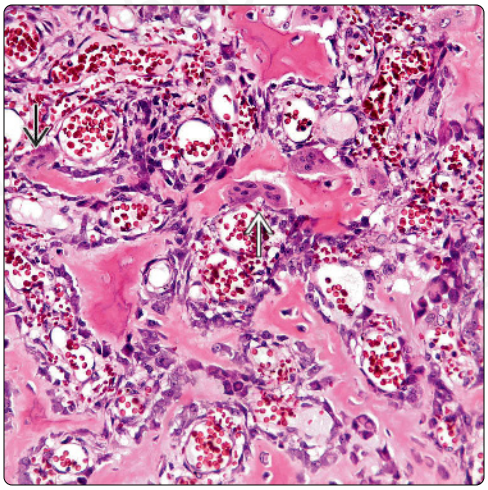


**(Left)** *Low-power view shows margin of an osteoblastoma. The tumor contains abundant haphazardly interconnecting trabeculae of woven bone, which is sharply demarcated from the surrounding uninvolved cancellous and cortical bone.* **(Right)** *A sharp margin of an osteoblastoma is shown with adjacent cancellous bone. The cellular tumor contains many small neoplastic bony trabeculae with intervening loose fibrovascular tissue. The uninvolved bony trabeculae are large and well formed.*

### Woven Bone Trabeculae of Osteoblastoma

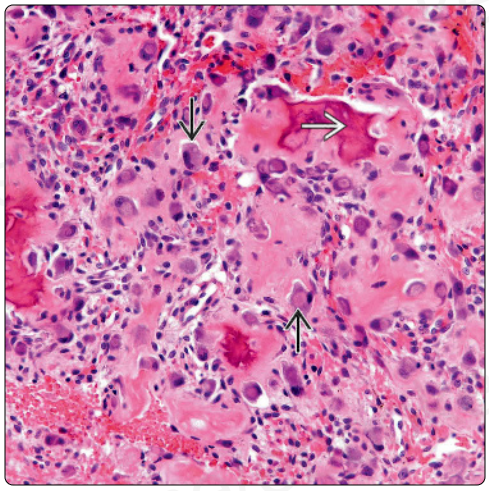


### Interconnecting Trabeculae of Bone

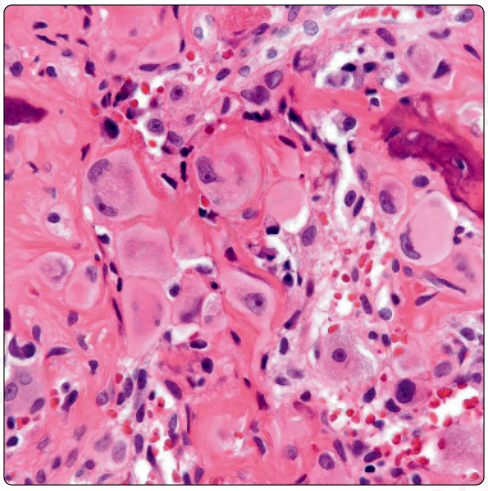


**(Left)** *An osteoblastoma is composed of irregular trabeculae of woven bone. The surfaces of the bone are rimmed by prominent osteoblasts. The intertrabecular space is filled with loose fibrovascular tissue. Many blood vessels are congested with red blood cells.* **(Right)** *Plump osteoblasts line the surfaces of the neoplastic bone. Scattered osteoclasts are also found on the surfaces of the woven bone. Many dilated, blood-filled capillaries course amongst the bony trabeculae.*

### Osteoblastoma With Epithelioid Cells

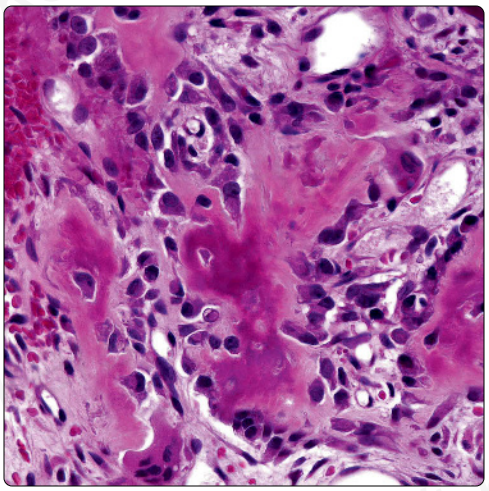


### Epithelioid Osteoblasts

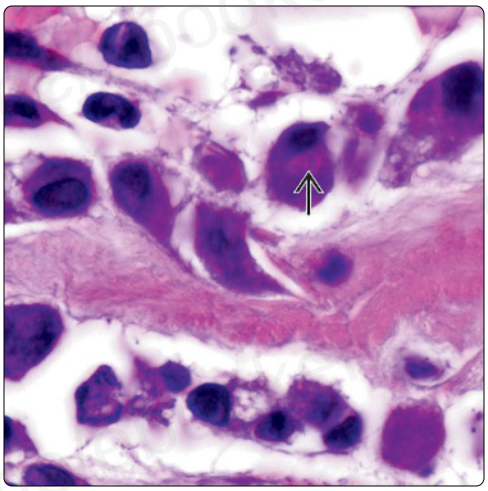


**(Left)** *A cellular osteoblastoma is shown with irregular trabeculae of woven bone. Scattered large epithelioid osteoblasts are present. Some of the neoplastic bone is mineralized and dark magenta in color.* **(Right)** *In an aggressive osteoblastoma composed of epithelioid osteoblasts, tumor cells are large, polyhedral, and contain abundant eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli. The neoplastic bone is coarse and lace-like in appearance.*

### Prominent Osteoblastic Rimming

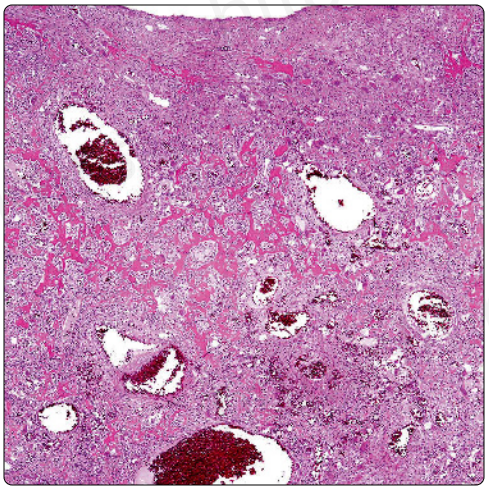


### Large Osteoblasts of Osteoblastoma

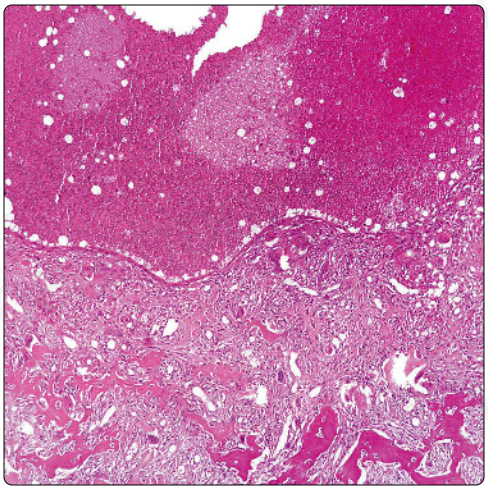


**(Left)** *Interconnecting trabeculae of bone are characteristic of osteoblastoma. The pink-purple bone is covered by a layer of osteoblasts. The nuclei of the osteoblasts tend to be polarized away from the bone-forming surfaces.* **(Right)** *High-power H&E shows neoplastic osteoblasts in an osteoblastoma. The polyhedral cells have abundant purple cytoplasm, which contain a prominent perinuclear Golgi apparatus ⇨ and eccentric nuclei. The pink tumor bone is woven in architecture.*

### Cystic Change

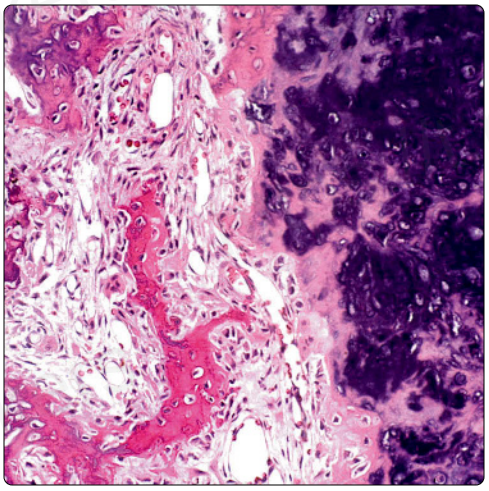


### Hemorrhagic Cystic Change

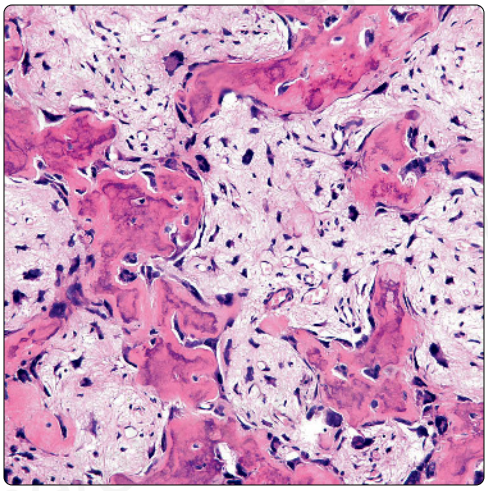


**(Left)** *Low-power view shows a cystic osteoblastoma. The cystic spaces are small and contain red blood cells. The solid portion consists of interconnecting trabeculae of woven bone. Cystic spaces can cause confusion with aneurysmal bone cyst.* **(Right)** *A cystic osteoblastoma is shown with a large cystic space filled with red blood cells and fibrin. Areas diagnostic of osteoblastoma are visible in the cyst wall consisting of haphazardly interconnecting trabeculae of woven bone lined by osteoblasts.*

### Osteoblastoma With Cartilage



### Pseudomalignant Change

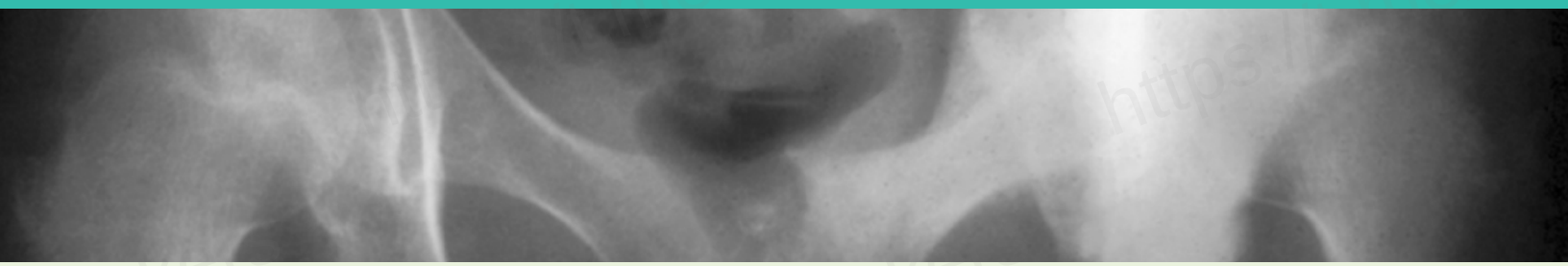


**(Left)** *An osteoblastoma with a nodular cartilaginous component is shown. The neoplastic blue cartilage is hyaline in type, moderately cellular, and adjacent to the bone-forming component of the tumor. The neoplastic bone has a trabecular pattern and is lined by osteoblasts.* **(Right)** *An osteoblastoma is seen with pseudomalignant change. Pseudomalignant features manifest as enlarged nuclei that are dark and hyperchromatic. Surrounding the bone is collagenous tissue with small blood vessels.*

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SECTION 2

# Malignant Bone-Forming Tumors




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# Conventional Osteosarcoma

KEY FACTS

## TERMINOLOGY

- High-grade malignant tumor in which neoplastic cells produce bone

## CLINICAL ISSUES

- Most common primary malignant tumor of bone; exclusive of hematopoietic malignancies
- Most patients are young, between 10-20 years of age
- Most commonly arises in long tubular bones
- Distal femur > proximal tibia > proximal humerus
- In older individuals, pelvis and axial skeleton are most common locations
- Limb salvage; complete excision with wide negative margins is optimal
- Preoperative chemotherapy often administered

## IMAGING

- Permeative and destructive lesion
- Centered around metaphysis of long bones
- Visible matrix present in 90% of cases

## MICROSCOPIC

- Admixture of 2 elements in varying proportions
  - High-grade sarcoma with epithelioid, plasmacytoid, fusiform, ovoid, small round cells, clear cells, mono- or multinucleated giant cells, or spindle cells
  - Bone matrix produced directly by tumor

## TOP DIFFERENTIAL DIAGNOSES

- Osteoblastoma
- Chondrosarcoma
- Myositis ossificans
- Giant cell tumor
- Metastatic carcinoma
- Ewing sarcoma
- Bizarre parosteal osteochondromatous proliferation
- Aneurysmal bone cyst

**OSA With Codman Triangle**



*A destructive tumor of the femur produces a mixed lytic and blastic pattern. The tumor invades the cortex and produces a Codman triangle. The soft tissue component has a cloud-like appearance.*

**OSA With Soft Tissue Extension**



*Classic osteosarcoma (OSA) arising in the distal femoral metadiaphyseal region is shown. The firm, tan-white, solid mass has transgressed the cortex and extended into the soft tissues. The growth plate is uninvolved.*

## TERMINOLOGY

### Abbreviations

- Osteosarcoma (OSA)

### Synonyms

- Osteogenic sarcoma; outdated term

### Definitions

- High-grade malignant tumor in which neoplastic cells produce bone

## ETIOLOGY/PATHOGENESIS

### Neoplastic Process

- Most OSAs arise de novo without known predisposing condition
- Others arise within diseased bone (so-called secondary OSA)
  - They can arise in patients with history of
    - Paget disease, radiation exposure, chemotherapy, trauma, foreign body (e.g., orthopedic implants), certain genetic abnormalities

### Genetic Susceptibility

- Hereditary retinoblastoma: Germline mutation in *RB1* gene
- Li-Fraumeni syndrome: Germline mutation in *TP53*
- Rothmund-Thomson syndrome
  - Skin lesions, photosensitivity, hypogonadism, psychomotor retardation, and various skeletal abnormalities

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Most common primary malignant tumor of bone; exclusive of hematopoietic malignancies
    - Accounts for ~ 20% of primary bone sarcomas
- Age
  - Most patients are young, between 10-20 years
    - Females usually younger than males, probably due to earlier skeletal development
  - 2nd peak occurs in patients > 50 years
- Sex
  - More common in males than females (1.3:1)

### Site

- Most commonly arises in long tubular bones
  - Distal femur > proximal tibia > proximal humerus
    - 50% of cases located in knee region
- In older individuals, pelvis and axial skeleton are most common locations
- < 10% occur in mandible and craniofacial bones

### Presentation

- Progressively enlarging, painful mass
  - Pain is deep seated and frequently noted months prior to diagnosis
  - Intensity of pain increases over time, eventually producing unremitting discomfort
- May appear as visible and palpable mass
- Overlying skin may be warm, erythematous, edematous, and cartographed by prominent engorged veins
  - Ulceration of skin secondary to pressure ischemia can occur
- Large tumors may restrict range of motion
- May cause joint effusions when tumor involves epiphysis or periarticular structures
- Patients with advanced cases may have weight loss and cachexia
- In 5-10% of cases, heralding event is pathologic fracture through tumor

### Laboratory Tests

- Elevated serum alkaline phosphatase

### Treatment

- Surgical approaches
  - Limb salvage; complete excision with wide negative margins is optimal
    - Biopsy tract is usually removed with tumor
  - Amputation is necessary if major vessels and nerves compromised, if tumor involves region that cannot be reconstructed, or if pathologic fracture or surgical intervention has contaminated large volumes of tissue
- Adjuvant therapy
  - Preoperative chemotherapy often administered
    - May diminish tumor in size
    - Tumor often undergoes more extensive mineralization and develops more developed pseudocapsule facilitating excision
    - Chemotherapeutic efficacy can be determined by histologic assessment of amount of necrosis induced in tumor
    - Tumor-induced necrosis of ≥ 90% considered good response and important prognostic indicator
- Drugs
  - Cisplatin, high-dose methotrexate, ifosfamide
- Radiation
  - Radiation as definitive treatment used for unresectable tumors because of size &/or site
  - Definitive radiation may be used to treat tumors in patients with widely metastatic disease who are considered incurable
  - Adjuvant radiation may be used if surgical excision is associated with positive margins

### Prognosis

- Relapse-free survival rates reported to vary from 50-80% (median: ~ 70%)
- Good responders to chemotherapy (≥ 90% necrosis after chemotherapy) have much better prognosis than poor responders

## IMAGING

### Radiographic Findings

- Permeative and destructive lesion; centered around metaphysis of long bones; poorly defined with lack of sclerotic rim
- Mixed lytic and blastic mass transgressing cortex and forming large soft tissue components
  - 90% extend into soft issue

- Visible matrix present in 90% of cases
  - Periphery of lesion usually less mineralized than central area
- Soft tissue components may have fine, cloud-like pattern of radiodensity
- In some instances, tumor is entirely lytic or sclerotic
  - Entirely lytic appearance is characteristic of telangiectatic variant
- Lower grade lesions tend to be more mineralized
- Periosteal reaction
  - Reactive woven bone is deposited between cortex and periosteum elevated by tumor
  - Appears either as multiple layers (onion skin) or radiating (sunburst) appearance
  - Codman triangle: Term used to describe periosteal reaction at diaphyseal end of tumor at angle created by cortex and elevated periosteum
- Rarely, imaging appears deceptively benign
- < 10% of lesions are diaphyseal
- Epiphyseal location; very rare

### MR Findings

- Heterogeneous metaphyseal mass; MR helpful in detecting skip lesions in same or adjacent bone
- Osteoid shows low signal on all sequences
- T1WI: Nonosteoid portions of tumor are near isointense to skeletal muscle
- Fluid-sensitive sequences: Tumor appears heterogeneous

### CT Findings

- Useful in defining bone matrix and when planning surgery and delineating extent of tumor

### Bone Scan

- Increased activity in primary tumor and metastasis

## MACROSCOPIC

### General Features

- Intramedullary; usually centered in metaphysis but can involve any portion of bone
- Tan-gray-white and gritty
- Tumors containing abundant mineralized bone are tan-white and hard
- Nonmineralized cartilaginous components are glistening, gray
  - May be mucinous if matrix is myxoid or more rubbery if hyaline in nature
- Areas of hemorrhage and cystic change; when extensive, produce friable, bloody, and spongy mass
- Tumor usually destroys overlying cortex and forms eccentric or circumferential soft tissue component displacing periosteum peripherally
- Dislodged periosteum becomes sharp interface between mass and bordering skeletal muscle and fat
- Layer of reactive bone at proximal and distal regions where periosteum 1st lifted from cortex
- Growth into joint space may occur
  - Growth may occur through synovium, via extension along cortical surface, or through tendoligamentous and joint capsule insertion sites
- Open growth plates often function as effective barriers to advancing tumors
  - Penetration of physis and invasion through epiphysis to base of articular surface occurs in some cases
- Skip metastases appear as intramedullary firm, ovoid, tan-white nodules located adjacent to or far from main mass
- Surface OSA

## MICROSCOPIC

### Histologic Features

- There are variety of different subtypes of OSAs depending on most prominent cell type
  - Giant cell rich, chondroblastic, osteoblastoma-like, telangiectatic, small cell, fibroblastic
  - This has no clinical significance (as long as tumor is high grade) but highlights how OSA can mimic variety of other bone tumors and vice versa
- Admixture of 2 elements in varying proportions
  - High-grade sarcoma with epithelioid, plasmacytoid, fusiform, ovoid, small round cells, clear cells, mono- or multinucleated giant cells, or spindle cells
  - Bone matrix produced directly by tumor
- Nuclei are hyperchromatic, central or eccentric in position
  - Brisk mitotic activity and prominent nucleoli are common
  - Degree of atypia variable but frequently severe
  - Numerous mitoses, commonly including atypical forms
- Cytoplasm is eosinophilic and variable in volume
- Tumor cells intimately related to surface of neoplastic bone
  - Tumor cells diminish in size and appear less atypical as they are surrounded and imprisoned by matrix
    - In heavily mineralized portions of tumor, neoplastic cells lack atypia
    - This phenomenon is referred to as "normalization"
- Neoplastic bone is woven in architecture and varies in quantity
  - Deposited as primitive, disorganized trabeculae producing coarse, lace-like pattern or broad, large sheets formed by coalescing trabeculae
  - Bone is frequently mineralized
  - In some instances, neoplastic bone uses preexisting trabeculae as scaffold
  - Neoplastic lamellar bone is very rare
- Bone is eosinophilic or basophilic and may have pagetoid appearance caused by haphazardly deposited cement lines
- Neoplastic cartilage, when present, is usually hyaline but may be predominately myxoid, particularly in tumors arising in jaw bones
- Malignant chondrocytes demonstrate severe cytologic atypia
- Fibroblastic foci manifest as cytologically malignant spindle cells arranged in herringbone or storiform pattern

## ANCILLARY TESTS

### Immunohistochemistry

- Immunoprofile is nonspecific
- SATB2 is nuclear transcription factor that stains osteoblasts
  - It is sensitive marker for OSA, but not specific, but can be helpful in problematic cases
- May be positive for keratin and epithelial membrane antigen

- Cartilaginous areas are positive for S100
- CD99 is frequently positive

### Genetic Testing

- Virtually all OSAs contain clonal chromosomal aberrations
- Aberrations are complex, comprising abundance of numerical and structural alterations
- No specific translocation has been identified in conventional OSA
- *TP53* and *RB1* are frequently mutated in OSAs
- Chromothripsis appears to be involved in pathogenesis in some OSAs
- Single-nucleotide variations demonstrate pattern of localized hypermutation (kataegis) in ~ 1/2 of pediatric OSAs

### Electron Microscopy

- Presence of eccentric nuclei, abundant and frequently dilated rough endoplasmic reticulum, and prominent Golgi centers suggest osteoblastic differentiation
- Features are not of diagnostic value

## DIFFERENTIAL DIAGNOSIS

### Fibrosarcoma

- Fibrosarcoma lacks tumor bone directly abutted by neoplastic cells
- Distinction between intraosseous fibrosarcoma and OSA is frequently an academic one
  - Chemotherapeutic regimens are similar

### Fracture Callus

- Bone is rimmed by osteoblasts
- Fracture site shows fibrocartilage, finding not seen in either OSA or chondrosarcoma
- Atypical mitotic figures are not seen
- Radiographic features frequently assist in making this distinction

### Osteoblastoma

- Distinction between osteoblastoma-like OSA and aggressive osteoblastoma is often challenging
- Features supporting diagnosis of OSA include
  - Infiltration of preexisting bony trabeculae
  - Large size (> 5 cm)
  - Atypical mitotic figures
  - Prominent and abundant lace-like tumor bone deposition
- Osteoblastoma typically shows interconnecting trabeculae of tumor bone lined by plump osteoblasts

### Chondrosarcoma

- In chondroblastic OSAs and some gnathic OSAs, bone may be scarce
- Extensive sampling will generally reveal foci of bone
- Cartilaginous tumor with marked atypia, particularly in 2nd and 3rd decades of life, is highly suspicious for OSA
- Presence of *IDH1* or *IDH2* mutations supports diagnosis of chondrosarcoma

### Dedifferentiated Chondrosarcoma

- Characterized by presence of low-grade cartilage juxtaposed to high-grade sarcoma (dedifferentiated component)
- Rarely, dedifferentiated component may be OSA

### Myositis Ossificans

- Both soft tissue and parosteal myositis ossificans may be mistaken for OSA
- Distinct zonal pattern is characteristic of myositis ossificans and is not seen in OSA
  - Grossly and on imaging, periphery of lesion is mineralized, whereas center lacks mineralization
  - Microscopically, central portion of lesion shows granulation tissue/nodular fasciitis-like appearance, whereas periphery shows woven bone lined by osteoblasts, with outermost layer of lamellar bone in mature lesions

### Giant Cell Tumor

- Reactive woven bone frequently found at periphery of lesion
- Unlike OSA, bone in giant cell tumor is lined by osteoblasts and not atypical tumor cells

### Metastatic Carcinoma

- Metastatic breast and prostate carcinoma may evoke robust osteoblastic reaction
- Appropriate immunohistochemical studies assist in making this distinction

### Ewing Sarcoma

- Small cell variant of OSA may mimic Ewing sarcoma
- In most cases, FISH will demonstrate rearrangement of *EWSR1* gene

### Bizarre Parosteal Osteochondromatous Proliferation

- Typically arise on surface of short tubular bones of hands and feet
- Distinct zonation pattern: Overlying hypercellular cartilaginous cap and underlying woven bone

### Aneurysmal Bone Cyst

- May mimic telangiectatic OSA
- Cells in cyst wall not severely atypical

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- At least focal bone production by malignant cells is necessary to render diagnosis of OSA
- Ancillary tests do not help in identifying bone
- Distinction between bone and nonosseous collagen may be difficult and, at times, arbitrary
- Delicate, lace-like deposition of mineralized eosinophilic matrix is highly suggestive of neoplastic bone

### Assessment of Chemotherapy Effect

- Complete (grade 4) or near complete (grade 3) > 90% necrosis of tumor is associated with survival advantage
- Assessment of necrosis should be performed by histologically evaluating central slice of tumor and sampling remaining 2 halves

## Histologic Types of Conventional Osteosarcoma

| Histologic Subtype | Histologic Characteristics | Differential Diagnosis |
|---|---|---|
| Osteoblastic and osteoblastoma-like variant | Abundant osteoid deposition | Osteoblastoma |
| Chondroblastic | Cartilaginous component predominates | Chondrosarcoma |
| Fibroblastic | Spindle cell component predominates | Fibrosarcoma |
| Giant cell rich | Osteoclast-type giant cells predominate | Giant cell-rich tumors, such as giant cell tumor |
| Small cell | Small cells predominate | Ewing sarcoma, lymphoma |
| Chondromyxoid fibroma-like variant | Resembles chondromyxoid fibroma | Chondromyxoid fibroma |
| Chondroblastoma-like variant | Resembles chondroblastoma | Chondroblastoma |

*These histologic subtypes are not associated with specific biological behavior.*

## Comparison of Conventional Osteosarcoma With Biologically Distinct Variants of Osteosarcoma

| | Conventional Osteosarcoma | Parosteal Osteosarcoma | Well-Differentiated Intramedullary Osteosarcoma | Osteosarcoma of Craniofacial Bones |
|---|---|---|---|---|
| Age | Peak incidence: 10-20 years | Peak incidence: 3rd decade | 2nd-5th decades | 3rd-4th decades |
| Sex | M > F | F > M | M = F | M = F |
| Common bone involved | Distal femur, proximal tibia, proximal humerus | Distal femur, proximal tibia, proximal humerus | Femur, tibia | Mandible and maxilla |
| Imaging | Destructive lytic/blastic metaphyseal lesion | Densely mineralized tumor on surface of bone | Intramedullary densely mineralized | Similar to conventional osteosarcoma |
| Characteristic histological features | High-grade sarcoma with osteoid matrix | Well-formed trabeculae of woven bone surrounded by mildly to moderately atypical cellular spindle cell proliferation in collagenous stroma | Well-formed trabeculae of woven bone surrounded by mildly to moderately atypical cellular spindle cell proliferation in collagenous stroma | Predominantly chondroblastic osteosarcoma; rarely well-differentiated osteosarcoma |
| Prognosis | Relapse-free survival: 70% | Very favorable; 5-year survival: 91-100%; 10-year survival: 80% | Favorable with very low risk of metastasis | Favorable compared to conventional osteosarcoma; lower incidence of metastasis |
| Therapy | Combinations of surgery, chemotherapy, and radiotherapy | Surgery alone | Surgery alone | Combinations of surgery, chemotherapy, and radiotherapy |

## Histologic Grading of Effect of Preoperative Chemotherapy on Primary Osteosarcoma

| Grade | Effect of Preoperative Chemotherapy |
|---|---|
| 1 | Little or no effect identified |
| 2 | Areas of acellular tumor osteoid, necrotic, &/or fibrotic material attributable to effect of chemotherapy with other areas of histologically viable tumor (≥ 10%) |
| 3 | Predominant areas of acellular tumor osteoid, necrotic, &/or fibrotic material attributable to effect of chemotherapy with only scattered foci of histologically viable tumor cells identified: < 10% viable tumor |
| 4 | No histologic evidence of viable tumor identified within entire specimen |

*Grades 3 and 4 indicate a favorable response. The adjuvant chemotherapy may be altered in cases with grades 1 and 2 responses.*

- Extent of necrosis on preoperative chemotherapy may be used to alter postoperative regimen

## SELECTED REFERENCES

1. Chen X et al: Recurrent somatic structural variations contribute to tumorigenesis in pediatric osteosarcoma. Cell Rep. 7(1):104-12, 2014

### Very Large Tumor: Humerus



### Swelling and Hyperemia



**(Left)** *This adolescent boy has a gigantic mass in the proximal humerus distorting the shoulder region. The overlying skin is attenuated, and large veins that feed and drain the tumor are visible. Joint motion is limited and severe pain is constant. (Courtesy C. Beukes, MD.)* **(Right)** *OSA of the proximal humerus producing swelling and hyperemia of the overlying skin is shown. There is a healing, linear, vertical biopsy scar located anteriorly. The tumor causes constant, deep-seated pain.*

### Lace-Like Radiodensity

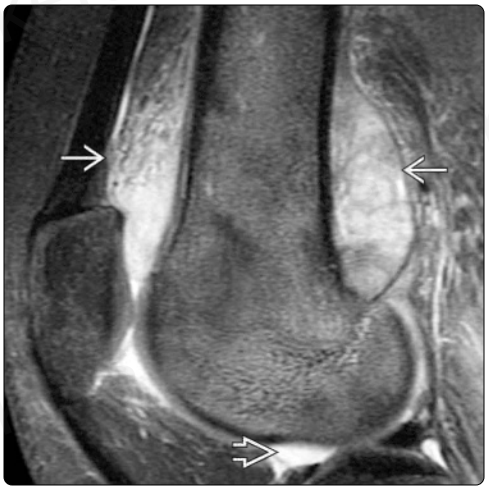


### Femoral OSA

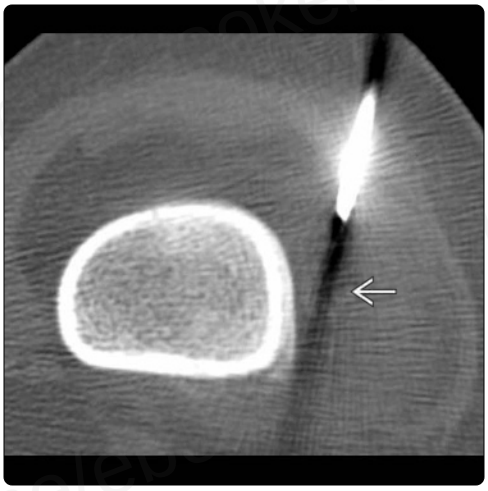


**(Left)** *AP radiograph shows an OSA of the distal femoral lateral metaphysis producing a lace-like pattern of radiodensity in the soft tissues and extending into the epiphysis, as demonstrated by the faint sclerosis of the lateral femoral condyle.* **(Right)** *T1-weighted MR shows that the OSA is much more extensive than suggested by the radiograph. It extends into the intercondylar region, at the origin of the anterior cruciate ligament, proximally in the marrow to the top of the image, and into the soft tissues.*

### Soft Tissue Extension



### Faint Soft Tissue Mineralization



**(Left)** *Sagittal T2-weighted MR shows an OSA permeating the distal femur extending both anteriorly and posteriorly, contacting the synovium. A joint effusion is present.* **(Right)** *Axial CT performed at the time of biopsy shows an OSA with faint mineralization in the soft tissue component beneath the tip of the biopsy device. Most of the mass is of low attenuation, which is not unusual due to the high water content of the poorly differentiated tissue. The intramedullary component is extremely subtle.*

**Pathologic Fracture of Femur**



**Pathologic Fracture**

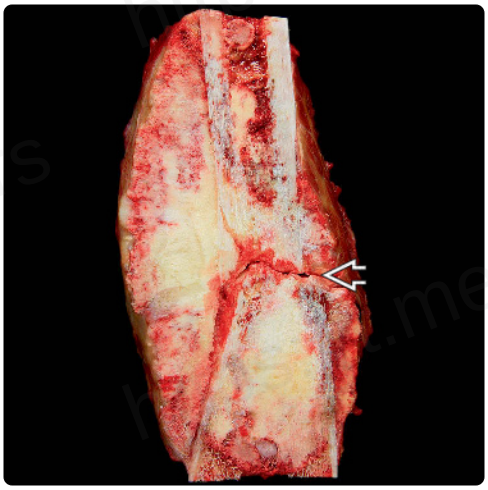


**(Left)** *This OSA of the distal femoral diaphysis and metaphysis has undergone pathologic fracture resulting in angulation of the bones. The poorly defined tumor is subtly radiodense and is associated with a large soft tissue mass.* **(Right)** *Coronal T1-weighted contrast-enhanced MR shows a large OSA in the femur, which has fractured. The tumor extends through the cortex and invades the adjacent soft tissues, and this component has an enhancing periphery.*

**OSA With Fracture**



**Pathologic Fracture**



**(Left)** *Close-up view shows a fracture through an ill-defined OSA involving the femoral shaft. Poorly organized mineralized tissue is seen around the fracture site and within the femur. The mineralized tissue does not show the layered structure that would be expected from simple callus.* **(Right)** *This OSA has caused a pathologic fracture of the distal femur. The tan-white solid tumor erodes the cortex and forms a large soft tissue mass that spans the fracture site.*

**Oblique Fracture Through Diaphysis**



**Pathologic Fracture With Hemorrhage**

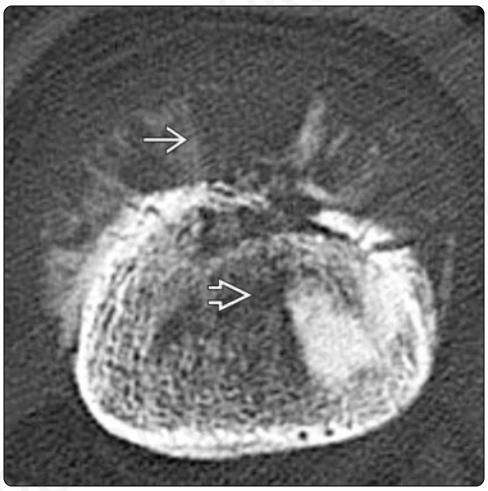


**(Left)** *Lateral radiograph of the femur in a child with open growth plates shows an oblique fracture through the proximal end of the distal diaphysis. The fracture extends through an OSA that has produced endosteal cortical thinning as well as faint medullary mineralization.* **(Right)** *Corresponding resection specimen shows the displaced fracture of the femoral diaphysis. The OSA is sclerotic with surrounding areas of hemorrhage.*

**Codman Triangle**

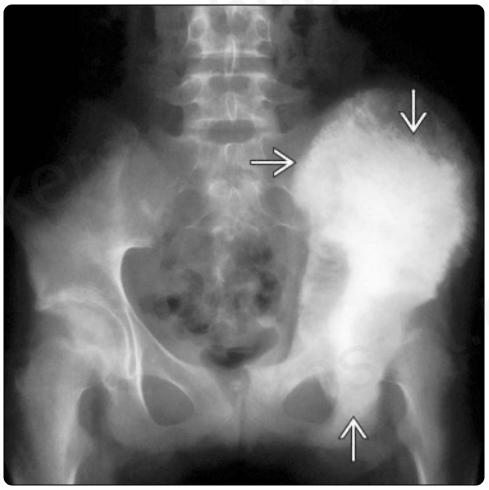


**Sunburst Pattern**

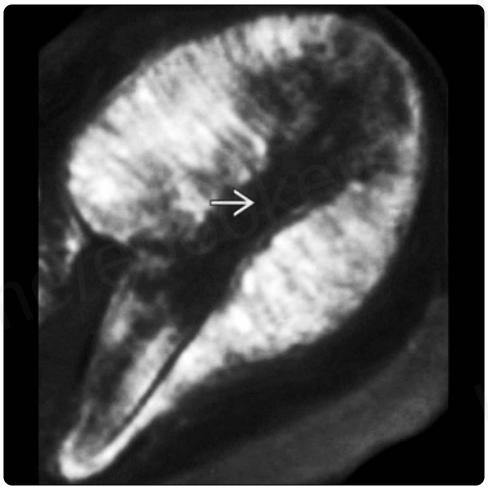


**(Left)** *Sagittal reformation CT demonstrates a bone-forming tumor of the metaphysis of the femur with a "sunburst" and Codman triangle periosteal reaction extending anteriorly. The tumor extends from the distal diaphysis to the growth plate.* **(Right)** *This OSA transgresses the cortex, producing a sunburst pattern characterized by trabeculae of bone radiating outward from a central region. The unmineralized tumor is of lower attenuation than muscle.*

**Densely Sclerotic OSA of Pelvis**



**Hair-on-End Pattern**

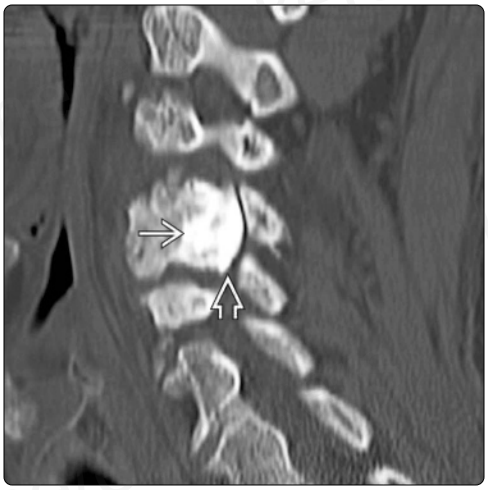


**(Left)** *AP radiograph of the pelvis shows an extremely large and densely sclerotic OSA of the left pelvis.* **(Right)** *Axial T2-weighted MR shows virtually no signal from within the intraosseous parts of the tumor due to almost complete mineralization. A large soft tissue mass surrounds the bone with a radiating hair-on-end pattern (perpendicular to bone) of signal "stripes" representing linear mineral deposits.*

**OSA of Cervical Spine**

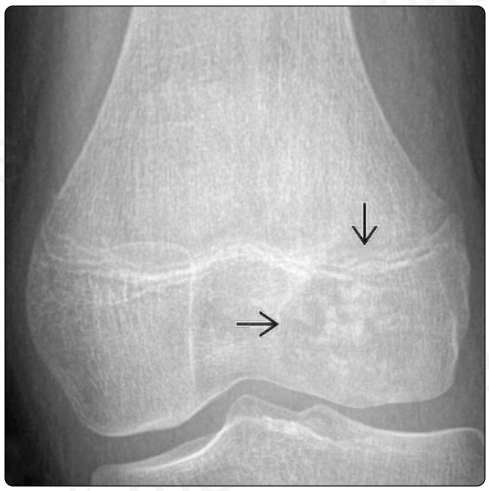


**Densely Mineralized OSA**

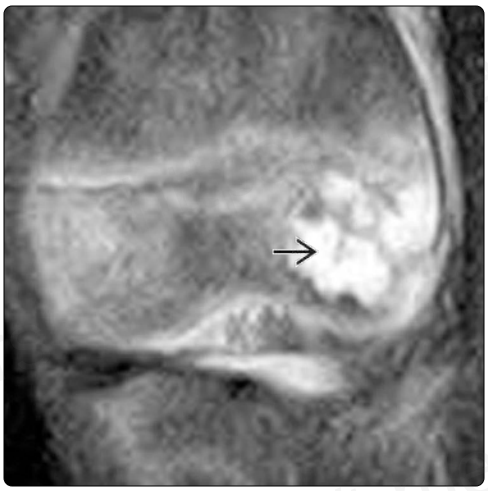


**(Left)** *Axial CT scan shows an OSA arising from the lateral mass of C4. The tumor is focally densely mineralized and has smooth soft tissue margins suggesting relatively slow growth.* **(Right)** *Reformatted sagittal CT scan shows an osteoblastic OSA of C4 that replaces a portion of the vertebral body and extends into the pedicle. The tumor is densely mineralized and has extended through the cortex forming a soft tissue component within the spinal canal.*

**OSA of Epiphysis**



**OSA of Epiphysis**

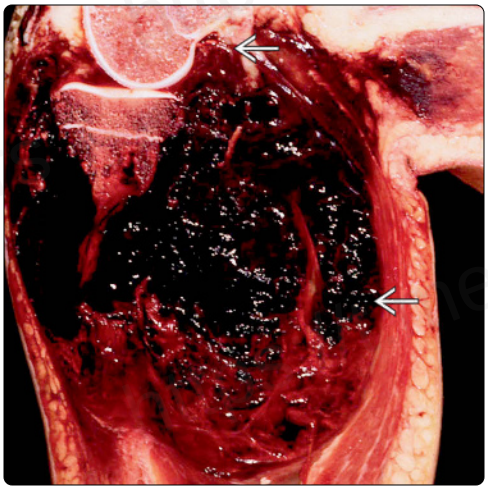


**(Left)** *AP radiograph of the knee shows a very rare epiphyseal origin of an OSA. The tumor appears to be confined to the bone of the lateral femoral condyle, encroaches upon the growth plate, and is mostly lytic with focal ossification.* **(Right)** *Coronal T2-weighted MR shows that the nonmineralized parts of the OSA have extremely high signal intensity consistent with a high water content of the tissue. The tumor is confined to bone without soft tissue extension.*

**Cystic OSA**



**Hemorrhagic Telangiectatic OSA**

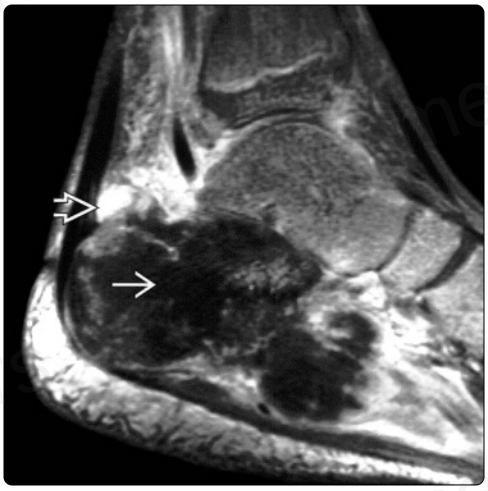


**(Left)** *Axial T2-weighted MR of the lower leg demonstrates a large telangiectatic OSA containing multiple fluid-fluid levels suggestive of an aneurysmal bone cyst. The tumor originates within the tibia, extends into the soft tissues, and is surrounded by a zone of edema.* **(Right)** *This telangiectatic OSA originates within the tibia and forms a large posterior soft tissue mass that extends proximally behind the femur. The tumor is cystic, friable, and hemorrhagic.*

**Dense OSA of Calcaneus**



**OSA of Calcaneus**



**(Left)** *Oblique radiograph, unfortunately underexposed, demonstrates a densely bone-forming lesion of the calcaneus. At the lower end of the image, mineralized tumor is visible in the soft tissues lateral and dorsal to the calcaneus.* **(Right)** *Sagittal T2-weighted MR of the calcaneal OSA shows the densely mineralized parts of the tumor as areas of very low signal intensity (black). Peripherally located nodules of high signal intensity represent less mineralized parts of the tumor.*

### Sclerotic and Lytic OSA



### Mineralized and Lytic OSA

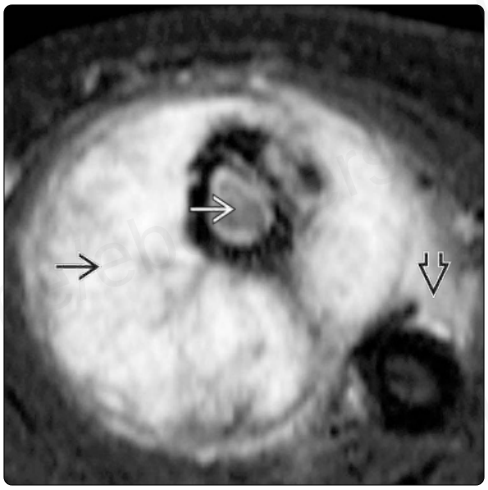


**(Left)** *Sagittal CT scan shows an OSA that arose in the distal femoral metaphysis. The intraosseous component is densely sclerotic, whereas the soft tissue element is less radiodense. Tumor involves the epiphysis and manifests as spotty calcifications.* **(Right)** *Sagittal T2-weighted MR shows the densely mineralized tumor within the femur as very low signal intensity. Extension into the epiphysis is seen. The soft tissue component has high signal intensity.*

### Sclerotic OSA of Distal Radius

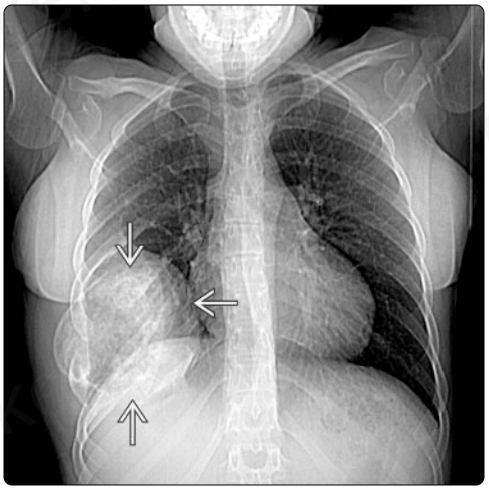


### Large Circumferential Soft Tissue Mass

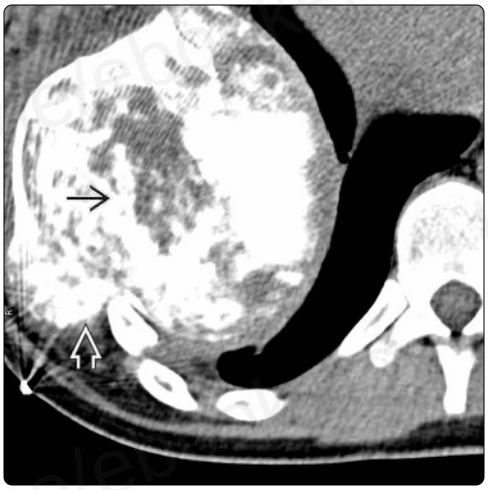


**(Left)** *AP radiograph of the wrist shows a densely mineralized tumor within the distal radius. The tumor extends to the subchondral bone plate, and its proximal margin is not included on the film. Note the mineralized soft tissue component.* **(Right)** *Axial T2-weighted MR of the distal forearm shows a very large mass arising from within the radius and forming a prominent circumferential soft tissue component. The tumor overgrows the neighboring portion of the ulna.*

### OSA of Rib

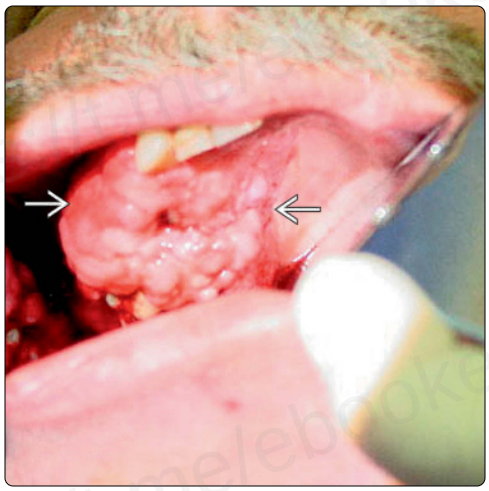


### Very Large OSA of Rib

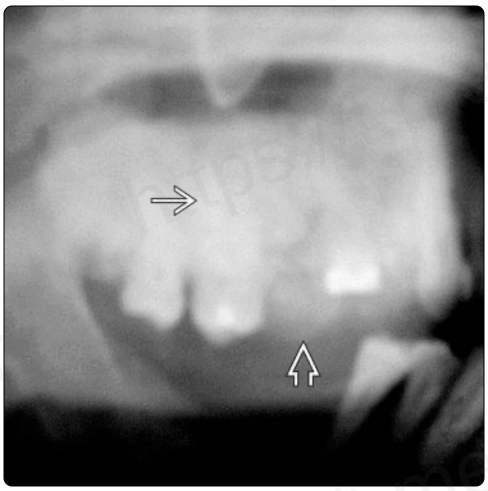


**(Left)** *PA chest radiograph shows a large lesion arising from the 7th rib. The bone lesion is surrounded by a large soft tissue component. The uninvolved lung fields are unremarkable.* **(Right)** *Axial CT shows a large heterogeneous OSA that destroys a rib and is associated with a large mineralized mass protruding into the chest. The mass is relatively well circumscribed and extends into the posterior chest wall soft tissues. The lung field is clear.*

**Swollen and Ulcerated OSA of Maxilla**

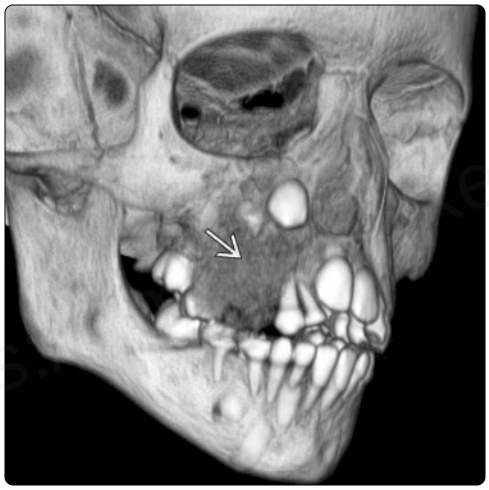


**Sclerotic OSA of Maxilla**

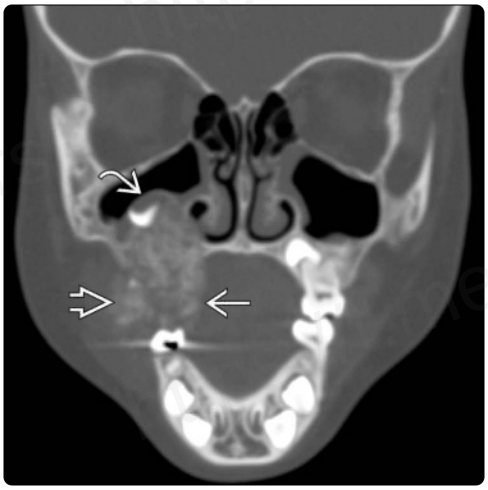


**(Left)** *An OSA of the maxilla distorts the overlying gingiva of the hard palate, which is swollen, irregular, and focally ulcerated. The tumor has grown over the previous several months and has interfered with mastication.* **(Right)** *Lateral radiograph of the mouth demonstrates a densely sclerotic OSA of the maxilla surrounding the teeth and protruding into the palate between them. The tumor is poorly mineralized and involves the visualized alveolar portion of the bone.*

**Maxillary OSA**



**Mineralized OSA of Maxilla**



**(Left)** *3D reformat of a CT scan demonstrates an OSA of the maxilla that extends between the teeth into the oral cavity. The tumor has an irregular contour and is destructive.* **(Right)** *Coronal CT shows a mineralized OSA that arises in the maxilla and bulges into the maxillary sinus. The tumor has destroyed the involved teeth and bulges into the oral cavity and masticatory musculature. The mass is mineralized throughout much of its substance.*

**Skip Metastases**



**Skip Metastases Hot on Bone Scan**



**(Left)** *OSA arising in the distal femoral metaphysis and epiphysis manifests as a poorly defined radiodense mass that appears to be confined to the bone. Separate oval mineralized nodules are seen more proximally, representing skip metastases, a poor prognostic finding.* **(Right)** *Radioisotope bone scan demonstrates a large focus of abnormal uptake in the distal femur as well as several foci within the more proximal parts of the bone that are skip metastases.*

### Cloud-Like Pattern of Mineralization



### Intracortical OSA



**(Left)** *AP radiograph of the knee shows an OSA of the distal femur. The location is markedly eccentric, raising the possibility that the lesion may have arisen in the cortex or periosteum. Note the subtle, cloud-like pattern ➡ of mineralization exhibited by the soft tissue component.* **(Right)** *Axial CT of the distal femoral metaphysis shows a very rare OSA that appears to have arisen in the cortex. The tumor involves the medullary cavity and bulges into the soft tissues.*

### OSA of Calvarium



### Tan-Pink and Hemorrhagic OSA

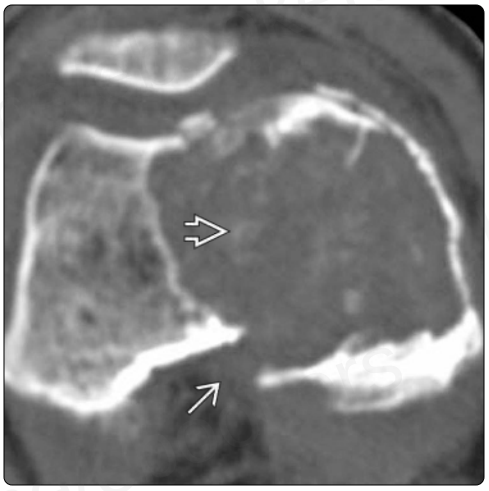


**(Left)** *Specimen radiograph of a resected portion of the calvaria shows a destructive lytic lesion ➡ that invades the overlying soft tissues. The margins are poorly defined and the soft tissue component has a fine, cloud-like pattern of mineralization ➡.* **(Right)** *This large OSA arises in the skull ⇨, extends into the soft tissues, and has ulcerated the skin. The pink-tan tumor is focally hemorrhagic and has a component that transgresses the cortex and displaces the meninges ➡.*

### Condylar OSA



### Femoral OSA With Pathologic Fracture

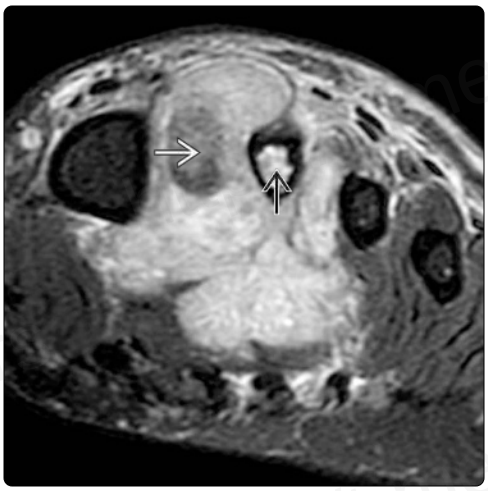


**(Left)** *AP radiograph shows that the medial femoral condyle has been expanded by a lytic and focally mineralized lesion that extends to the subchondral bone. In these respects, the lesion resembles a giant cell tumor. The involved cortex is thinned ➡ and the proximal margin ➡ is relatively well delineated.* **(Right)** *Axial CT scan through the distal femur shows a pathological fracture through an OSA. There is a posterior soft tissue mass ➡ and foci of tumor mineralization ➡.*

### OSA of Foot



### Metatarsal OSA



**(Left)** *Axial CT scan of the foot shows an OSA arising from the 2nd metatarsal. The bone is destroyed, and a soft tissue mass containing some mineralization is present. There is periosteal new bone arising from the surface of the 3rd metatarsal.* **(Right)** *Axial T2-weighted MR shows an OSA that arises in and destroys the 2nd metatarsal. The tumor has large dorsal and ventral soft tissue components and invades the 3rd metatarsal, features not well seen on the CT scan.*

### Large OSA of Distal Femur



### Postchemotherapy Radiographic Features



**(Left)** *Pretreatment lateral radiograph shows a large OSA involving the distal femur. The poorly defined, mineralized tumor invades the growth plate and has a large circumferential soft tissue component. Note the Codman triangle.* **(Right)** *After chemotherapy, the OSA shows a greater degree of mineralization and appears to be confined by a radiodense pseudocapsule. This translates into the tumor being better defined and more easily excised at surgery.*

### Densely Mineralized OSA

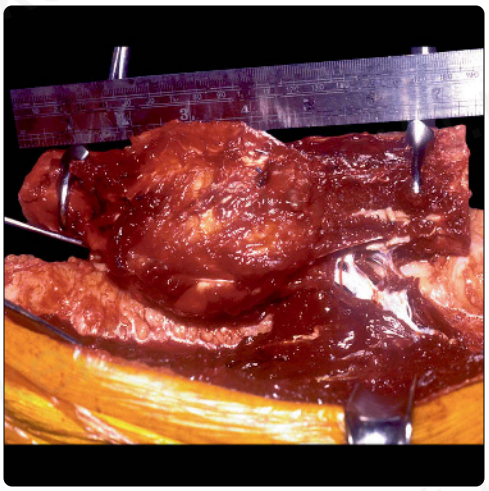


### Limb-Sparing Resection of OSA

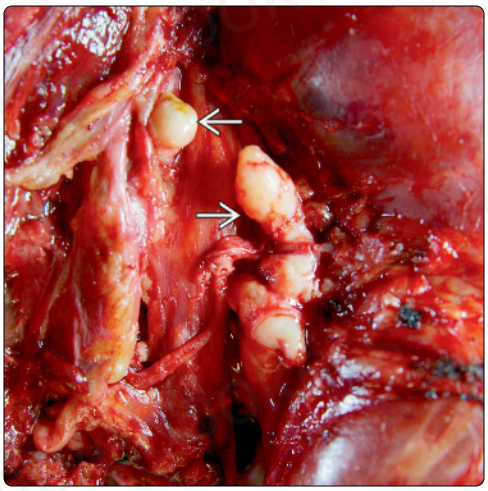


**(Left)** *AP radiograph of the distal femur shows a large and densely mineralized OSA of the metaphysis and diaphysis extending at least to the level of the growth plate. The tumor has a large soft tissue component.* **(Right)** *A limb-sparing resection of the OSA was performed with reconstruction of the distal 1/2 of the femur by a custom metal implant. Because the tumor invaded the epiphysis and possibly the joint, the knee was resected and a total joint replacement was performed.*

### Intraoperative Gross Photo



### Venous Invasion



**(Left)** *This OSA of the diaphysis of the femur is in the process of being resected. The ends of the bone have been transected, and the tumor is being lifted out of the surgical bed. The tumor is covered by a layer of skeletal muscle. A ruler measures the excised bone for purposes of reconstruction.* **(Right)** *This resection shows a large chondroblastic OSA of the pelvis covered by skeletal muscle. Multiple worm-like structures of tumor fill veins ➡ and are a poor prognostic finding.*

### Cadaveric Osteochondral Allograft

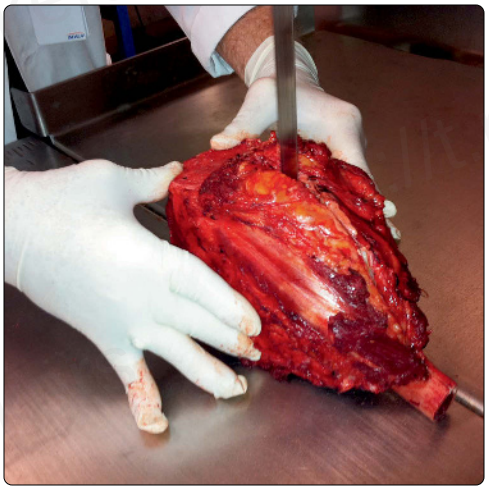


### Above-Knee Amputation

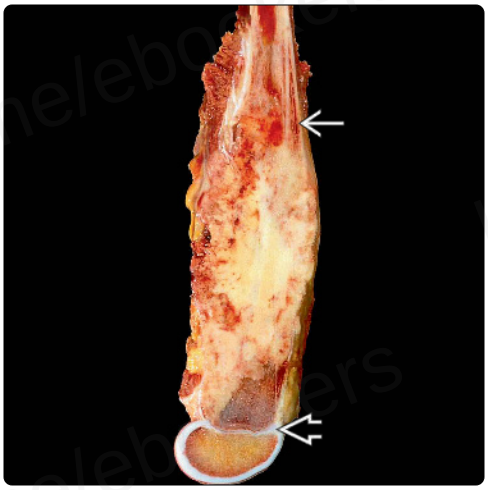


**(Left)** *An OSA of the distal femur has been resected by a limb salvage procedure, and the defect has been repaired by a cadaveric osteochondral allograft stabilized by a large metal plate and numerous screws. The osteosynthesis site appears to be fusing ➡.* **(Right)** *Although most OSAs are resected in a limb salvage manner to preserve function, amputation may be necessary when vital neurovascular structures are involved by tumor. An amputation with a prothesis can be very effective.*

### Resected OSA Bisected

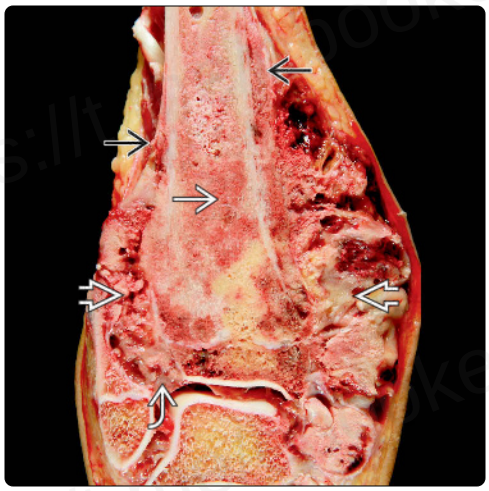


### Tan-White and Sclerotic OSA

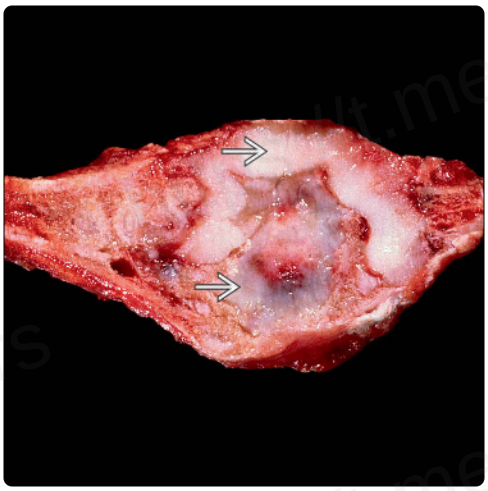


**(Left)** *A resected OSA should be bisected through the greatest dimension of the tumor in relation to the soft tissue and bone resection margins. A central slab of tumor should be processed, and 1 section per centimeter of the remaining hemispheres should be sampled.* **(Right)** *A tan-white OSA of the distal femur fills the medullary cavity and extends into the soft tissues. Note the Codman triangle located proximally ➡ and the intact growth plate ➡, which is not violated by tumor.*

## Large, Friable, and Hemorrhagic Tumor



## Gray-Glistening Chondroblastic OSA

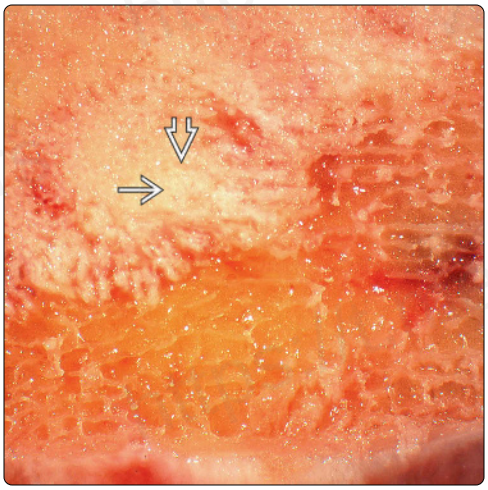


**(Left)** *An OSA involving the tibial distal metaphysis and diaphysis violates the growth plate and transgresses the cortex, forming a large, circumferential soft tissue mass. The friable, hemorrhagic tumor extends into the ankle joint and attenuates the skin along the medial aspect. A conspicuous Codman triangle is present.* **(Right)** *A chondroblastic OSA of the rib expands the bone. The cartilaginous element is blue-tan-white and is the predominant component of the tumor.*

## Cystic Telangiectatic OSA

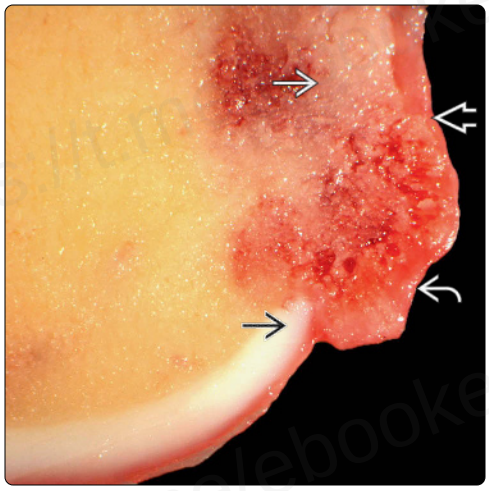


## Infiltrative Growth Pattern



**(Left)** *This telangiectatic OSA arises in the femoral distal metaphysis and is confined to the bone. The hemorrhagic tumor is composed of variably sized cysts that are filled with blood. The cysts are relatively well circumscribed, have an irregular contour, and are surrounded by a zone of erythema.* **(Right)** *Osteoblastic OSA involves the medullary cavity of the femur. The tan-white tumor grows with an infiltrative pattern and encompasses preexisting cancellous bone.*

## Intraarticular Extension

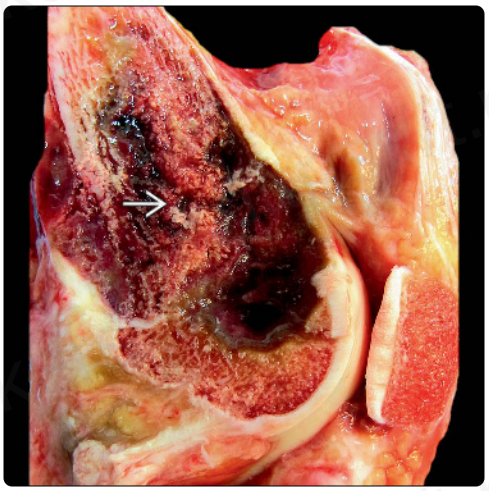


## Skip Metastasis



**(Left)** *An osteoblastic OSA of the distal femur extends into the epiphysis. The tumor infiltrates the medullary cavity, surrounds preexisting bony trabeculae, and involves the subchondral bone plate. The tumor enters the joint space by transgressing the synovium and overgrows the most posterior aspect of the articular cartilage.* **(Right)** *A skip metastasis in a patient with an OSA of the distal femoral metaphysis is shown. The tan-white tumor is confined to the medulla.*

### Hemorrhagic and Necrotic Tumor

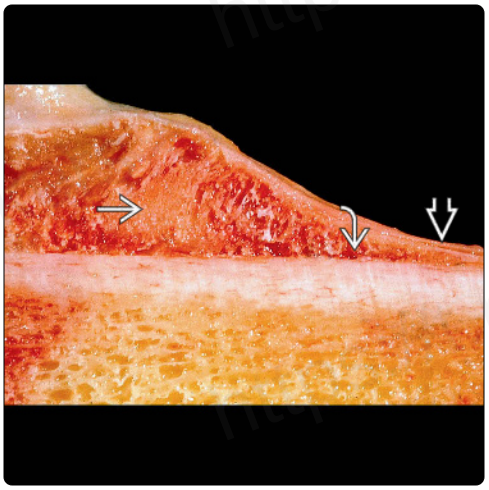


### OSA Is Skeletally Immature

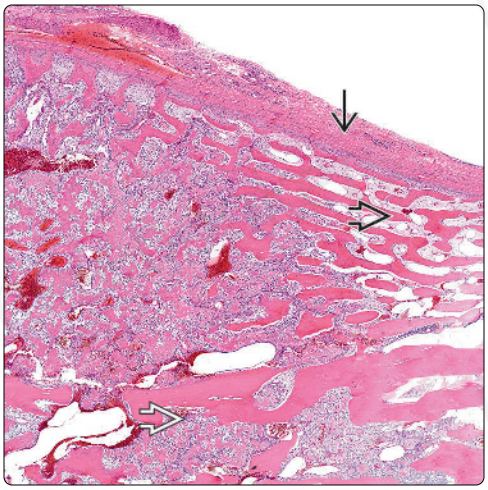


**(Left)** *OSA of distal femoral metaphysis extends into the epiphysis, which has been treated preoperatively with systemic chemotherapy. The tumor is significantly smaller than before chemotherapy and is hemorrhagic and tan-brown, features suggestive of necrosis.* **(Right)** *OSA of the radius arising in a skeletally immature individual is shown. The tumor is tan-white, involves the medullary cavity, destroys the cortex, and elevates the periosteum. Distally, it abuts the open growth plate.*

### Codman Triangle

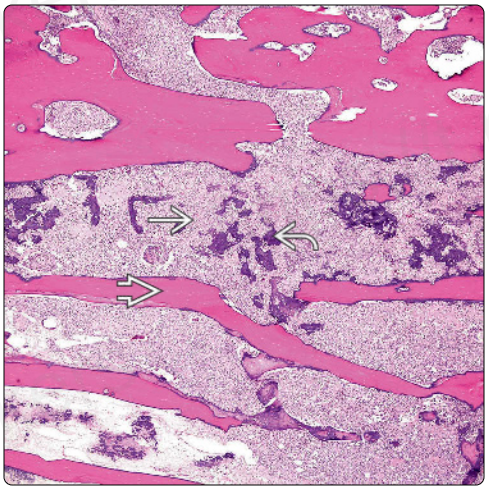


### Codman Triangle

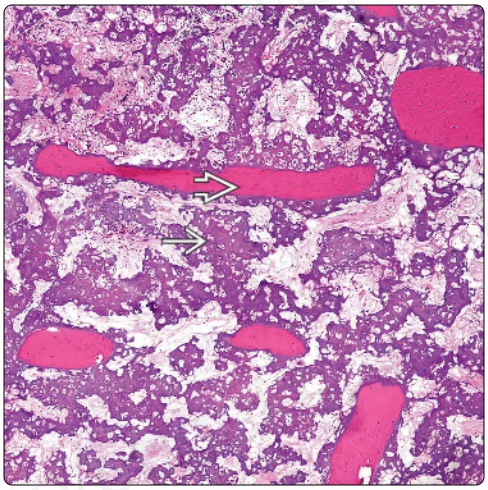


**(Left)** *This OSA of a long bone arises in the medullary cavity and extends proximally along the surface, raising the periosteum and forming a Codman triangle. The tumor has mechanically lifted the periosteum, which has deposited reactive bone during the process.* **(Right)** *An OSA infiltrates and fills the medullary cavity and transgresses the cortex. The tumor displaces the periosteum, which has deposited reactive bone forming a Codman triangle.*

### Permeative Growth Pattern

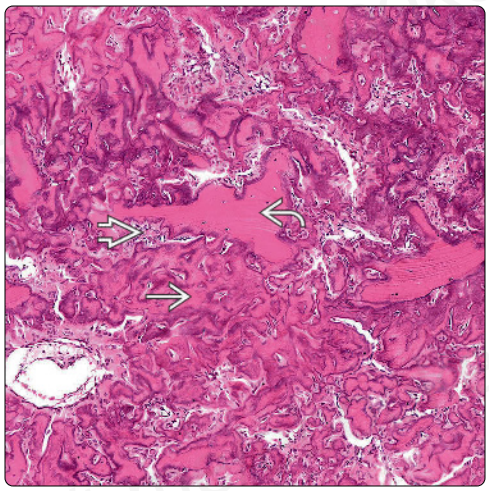


### Interconnecting Purple Trabeculae

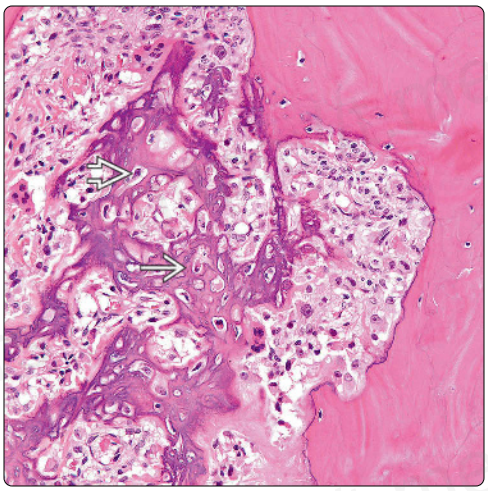


**(Left)** *A permeative growth pattern is typical of OSA. The tumor replaces the marrow and encases preexisting cancellous bone. The tumor is hypercellular and produces neoplastic bone, which is purple and appears as irregular, coarse trabeculae.* **(Right)** *Abundant neoplastic bone in the form of irregular interconnecting purple trabeculae of woven bone is characteristic of osteoblastic OSA. The tumor permeates the marrow and surrounds preexisting trabeculae.*

### Sclerosing OSA

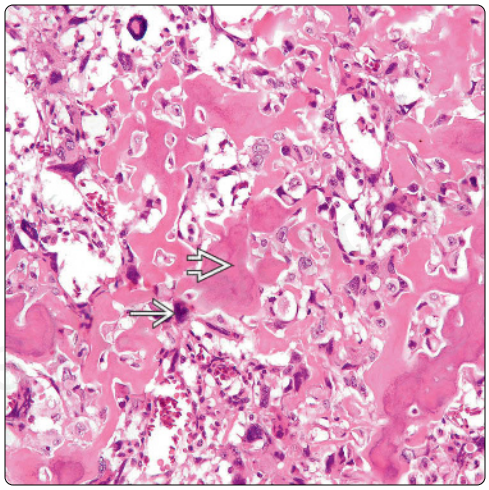


### Pink-Purple Woven Bone

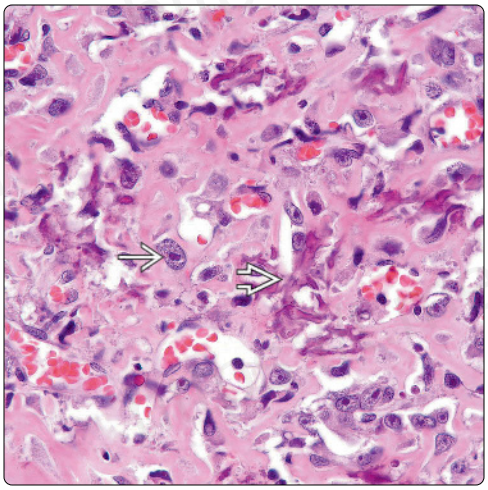


**(Left)** *Sclerosing variant of osteoblastic OSA contains tremendous amounts of mineralized neoplastic bone. The tumor bone is woven, coarse, and lace-like in appearance. The tumor cells fill the spaces in between the matrix. The preexisting trabeculae are encased by the tumor.* **(Right)** *Trabeculae of pink-purple woven bone typifies mineralized neoplastic bone in OSA. The tumor cells show moderate cytologic atypia, and those imprisoned by matrix are "normalized."*

### Pleomorphic Tumor Cells

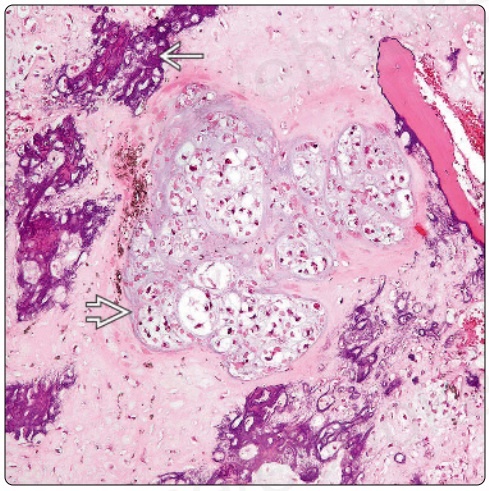


### Large Atypical Cells

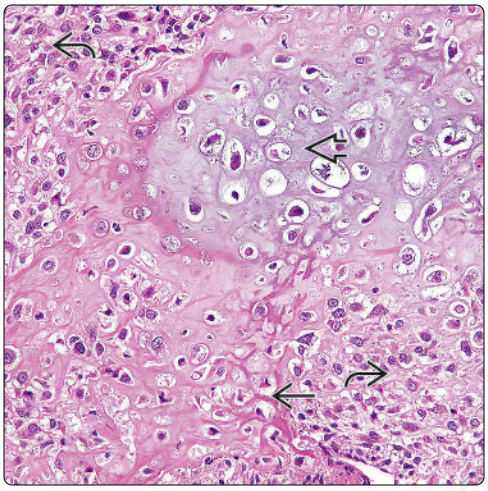


**(Left)** *Osteoblastic OSA is composed of pleomorphic tumor cells that contain enlarged hyperchromatic nuclei. The tumor cells are in intimate contact with coarse, lace-like neoplastic bone that is both unmineralized (osteoid) and mineralized (bone).* **(Right)** *The tumor cells in this OSA are large and have indistinct eosinophilic cytoplasm. The vesicular nuclei contain large nucleoli. The tumor cells are surrounded by eosinophilic tumor bone that is focally mineralized.*

### Neoplastic Bone and Cartilage

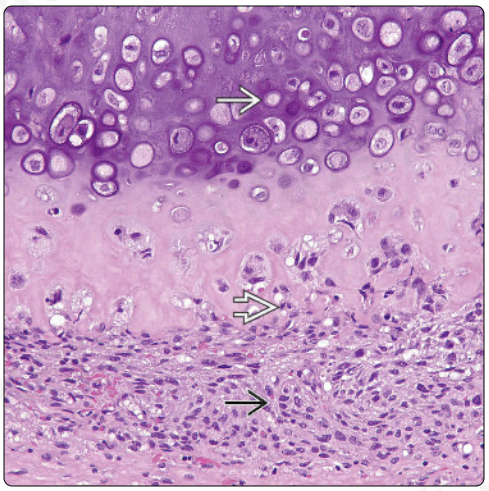


### Chondroblastic and Osteoblastic

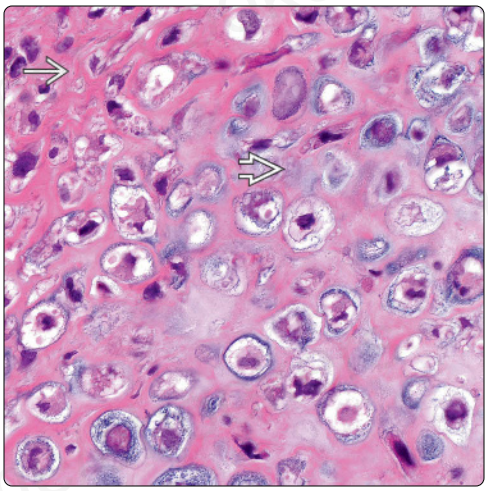


**(Left)** *Mixed osteoblastic and chondroblastic OSA contains both neoplastic bone and cartilage, and often the matrices merge into one another. The tumor bone has an irregular trabecular architecture, and the cartilage is often hyaline and hypercellular, demonstrating significant cytologic atypia.* **(Right)** *An example of a mixed osteoblastic and chondroblastic OSA shows neoplastic bone merging with neoplastic hyaline cartilage. Areas devoid of matrix are hypercellular and atypical.*

### Chondroblastic OSA

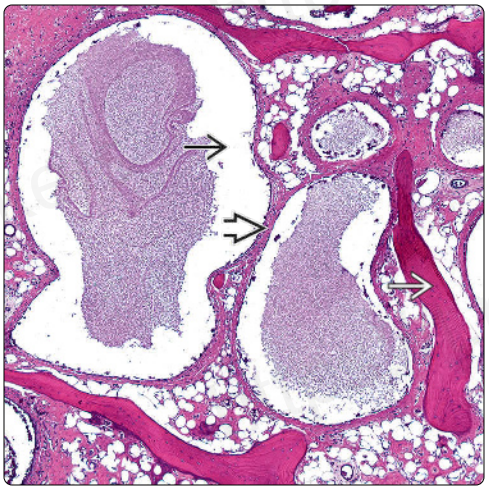


### Coarse, Lace-Like Tumor Bone

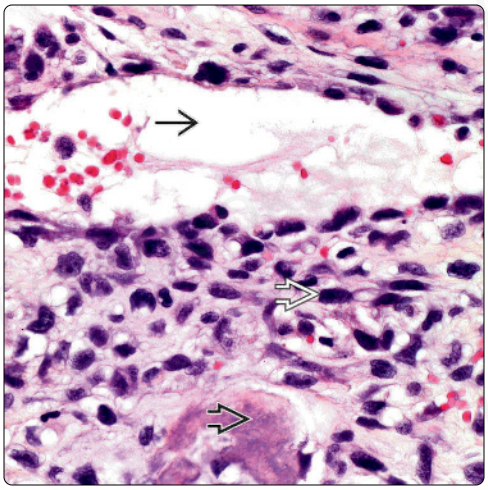


**(Left)** *Chondroblastic OSA can sometimes present as large nodules of neoplastic hyaline cartilage that transition into coarse, lace-like neoplastic osteoid. This in turn is surrounded by a hypercellular cuff of tumor cells that demonstrate atypical cytologic features and are histologically malignant.* **(Right)** *Coarse, lace-like tumor bone often merges into neoplastic cartilage in chondroblastic OSA. The cartilaginous component often shows severe atypia and mitoses.*

### Extensive Cystic Changes

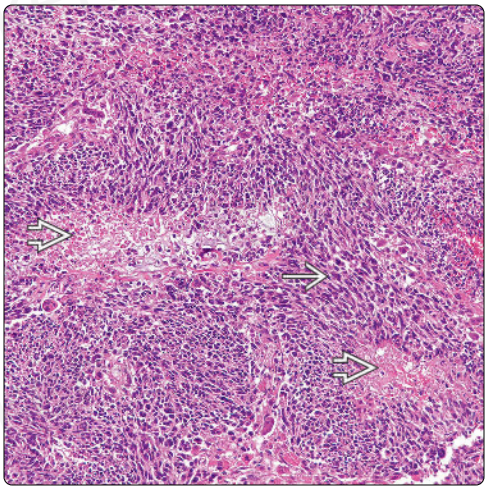


### Telangiectatic OSA

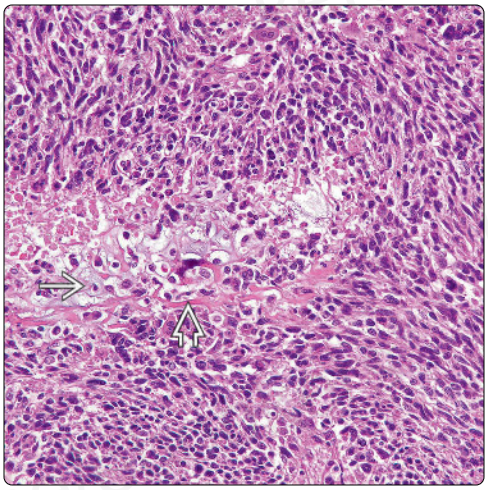


**(Left)** *Telangiectatic OSA is characterized by extensive cystic change. The tumor grows with an infiltrative pattern and encases preexisting bony trabeculae. The cysts may be filled with blood, and the cyst walls are of variable thickness. The tumor can mimic a vascular tumor and aneurysmal bone cyst.* **(Right)** *A small cyst in telangiectatic OSA contains red blood cells. The cyst wall contains cytologically malignant spindle cells and a focus of mineralized neoplastic bone.*

### Spindle Cells in Fibroblastic OSA

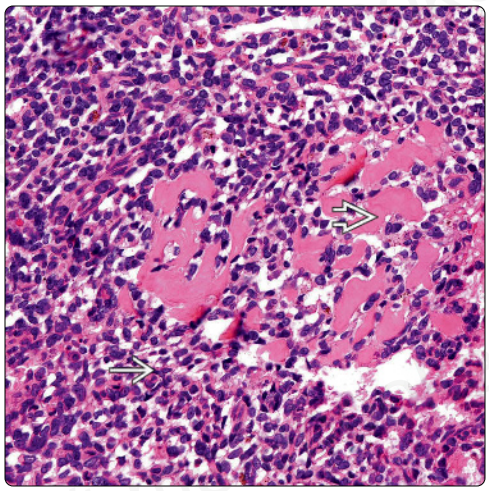


### Small Focus of Neoplastic Bone

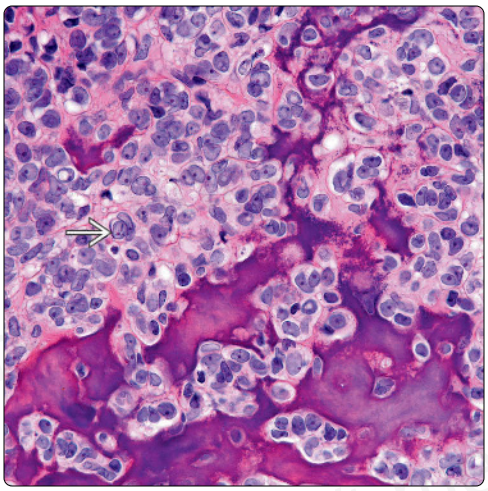


**(Left)** *Fibroblastic OSA usually contains cytologically malignant spindle cells arranged in intersecting fascicles that can have a herringbone or storiform appearance. In this case, the tumor cells demonstrate significant atypia, and there are foci of necrosis.* **(Right)** *The amount of neoplastic bone in OSA can be very variable. In this fibroblastic OSA, there is a small focus of neoplastic hyaline cartilage merging with coarse, lace-like tumor bone.*

### Small Cell OSA

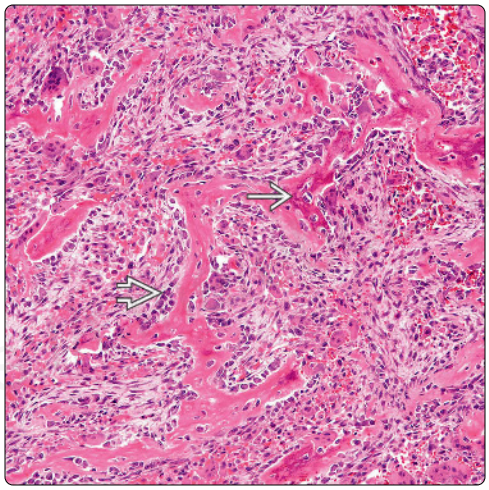


### Mimicking Ewing Sarcoma

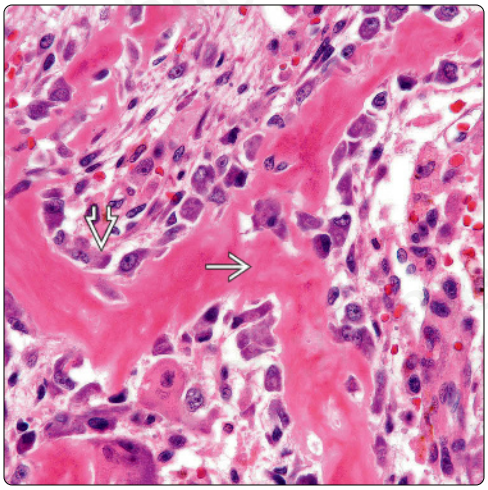


**(Left)** *Small cell OSA is a challenging diagnosis because the tumor can resemble other round cell malignancies, including sarcomas, carcinomas, and lymphomas. In this case, the small, round and ovoid cells grow in sheets and are intimately associated with eosinophilic tumor bone.* **(Right)** *In this small cell OSA, the round tumor cells have little cytoplasm and nuclei with fine chromatic and small nucleoli; these cells resemble those in Ewing sarcoma. The tumor bone is mineralized.*

### Mimicking Osteoblastoma

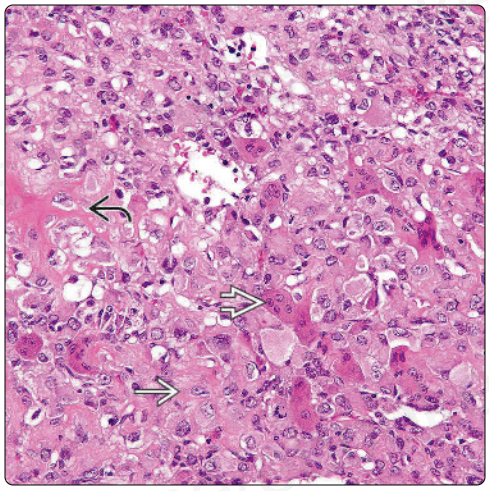


### Osteoblastoma-Like OSA

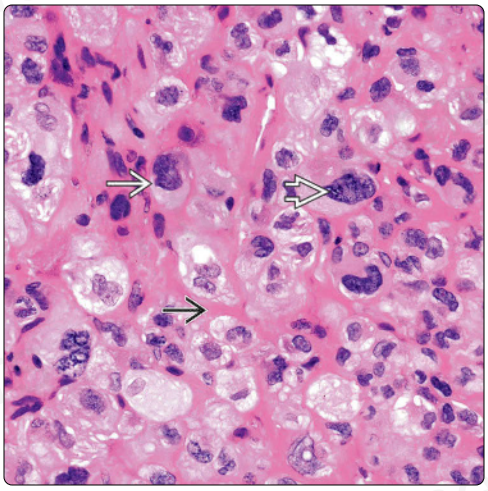


**(Left)** *Osteoblastoma-like OSA is difficult to diagnose because of its similarity to osteoblastoma. The neoplastic woven bone appears as well-formed trabeculae lined by a prominent layer of osteoblasts. There is often limited cytologic atypia. Infiltration of preexisting bone must be present to confirm the diagnosis.* **(Right)** *The tumor bone in osteoblastoma-like OSA is woven and well formed. The neoplastic osteoblasts do not demonstrate appreciable atypia.*

### Epithelioid Neoplastic Cells

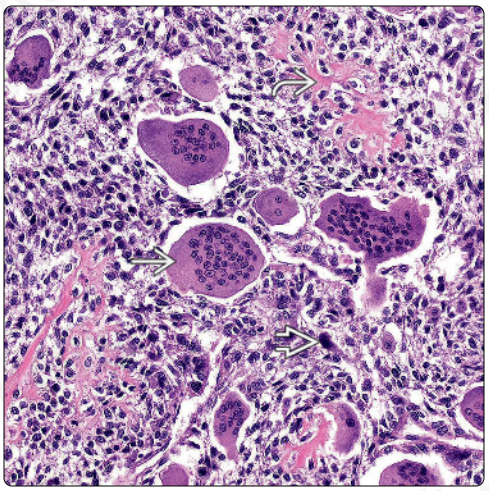


### Epithelioid OSA

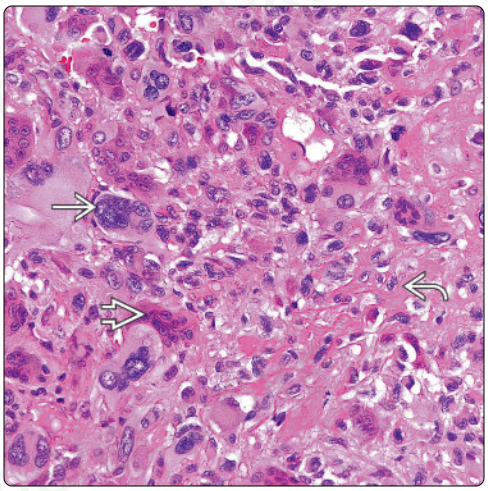


**(Left)** *In this OSA, the tumor cells are large and polyhedral (epithelioid) and have abundant eosinophilic cytoplasm and large atypical nuclei. Scattered throughout the tumor are nonneoplastic, osteoclast-like giant cells. The tumor bone is eosinophilic, coarse, and lace-like in appearance.* **(Right)** *This epithelioid OSA is composed of large polyhedral tumor cells with abundant eosinophilic cytoplasm and enlarged hyperchromatic nuclei. Tumor bone surrounds the cells.*

### Numerous Osteoclast-Type Giant Cells

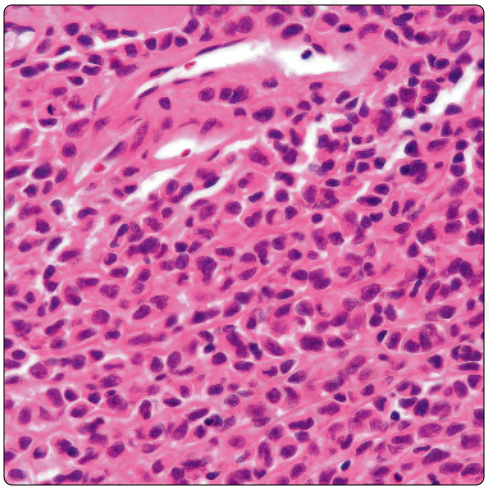


### Giant Cell-Rich OSA

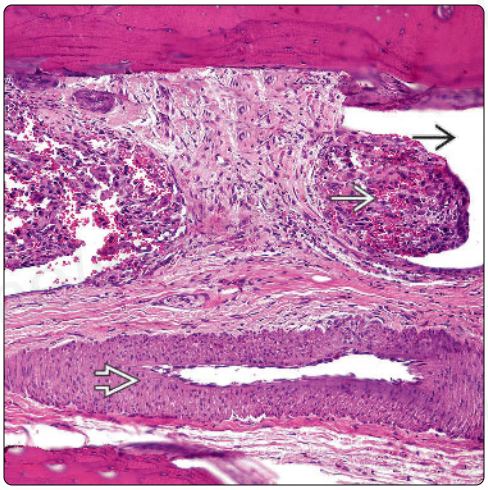


**(Left)** *In this giant cell-rich OSA, there are many large nonneoplastic osteoclast-like cells ➡ scattered throughout the tumor. Their presence can cause confusion with a giant cell tumor. The distinction is based on the presence of cytologically malignant tumor cells ➡ and neoplastic bone ➡.* **(Right)** *The tumor cells demonstrate severe atypia ➡ in this giant cell-rich OSA. The osteoclast-like cells ➡ are smaller than many of the tumor cells. Note the neoplastic bone ➡.*

### Chondroblastoma-Like OSA

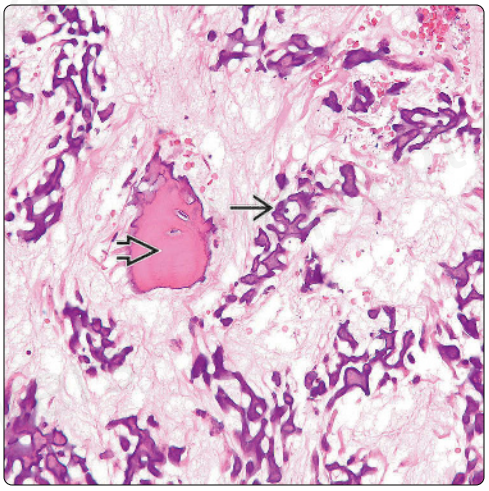


### Venous Invasion

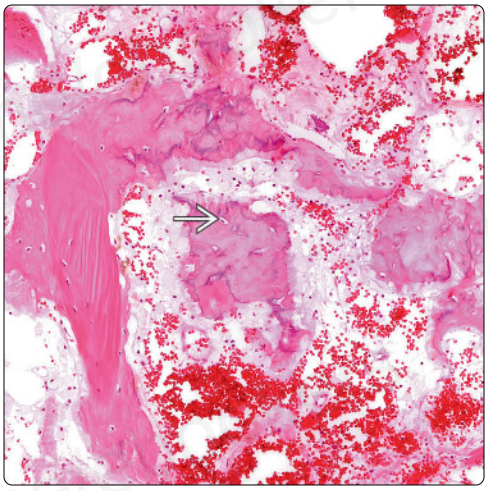


**(Left)** *Rare chondroblastoma-like OSA is shown. Tumor cells resemble those in chondroblastoma in that they are small and have moderate amounts of eosinophilic cytoplasm and irregular, grooved and cleaved nuclei. Neoplastic bone is not present.* **(Right)** *Emboli of OSA ➡ fill the lumen of this large vein ⇨. The artery ➡ is not involved. OSA usually disseminates hematogenously and infrequently enters lymphatics and spreads to lymph nodes.*

### Chemotherapy Effect



### Systemic Chemotherapy Response



**(Left)** *This high-grade osteoblastic OSA was treated with systemic chemotherapy. The tumor demonstrates an excellent response with necrosis of all of the tumor cells. The mineralized matrix ⇨ is still present and is a marker of areas previously inhabited by the neoplasm. Note the preexisting trabeculum ⇨.* **(Right)** *An osteoblastic OSA with a very good response to systemic chemotherapy is shown. The tumor cells are necrotic except for those that persist within the matrix ➡ like osteocytes.*

# Well-Differentiated Intramedullary Osteosarcoma

KEY FACTS

## TERMINOLOGY

- Low-grade osteosarcoma composed of bland, spindle-shaped cells and mature bone
- Similar in histologic appearance to surface low-grade osteosarcoma (parosteal osteosarcoma)

## CLINICAL ISSUES

- Represents ~ 1% of all osteosarcomas
- Develops during 2nd-5th decades of life
- Typically centered in medullary cavity of metaphysis or metaphyseal-diaphyseal region of long tubular bone
- Surgery alone since it is associated with low risk of dissemination
- Metastatic rate ~ 15%

## IMAGING

- Densely cloud-like and mineralized
- Poorly demarcated margins

## MACROSCOPIC

- Hard, gritty, tan-white

## MICROSCOPIC

- Mild to moderately cellular cytologically bland spindle cell component
- Neoplastic cells are intimately associated with long trabeculae or round islands of woven bone, which may have pagetoid appearance
- Grows with infiltrative pattern

## ANCILLARY TESTS

- Many stain for MDM2 and CDK4
- *MDM2* amplification can be detected by FISH

## TOP DIFFERENTIAL DIAGNOSES

- Fibrous dysplasia
- Desmoplastic fibroma
- Fibrosarcoma

**Poorly Defined Sclerotic Tumor** | **Hard Mass**

**(Left)** *The well-differentiated osteosarcoma involves the metadiaphyseal region of tibia. The tumor is radiodense and has poorly defined margins. The mass has not caused a periosteal reaction.* **(Right)** *Resected distal tibial tumor has replaced the majority of the distal tibial medullary cavity. The tumor encompasses the preexisting cancellous bone and has eroded through the cortex.*





**Sclerotic Tumor** | **Mass Filling Medullary Cavity**

**(Left)** *This osteosarcoma fills the medullary cavity of the proximal humerus and extends distally in the diaphysis. The tumor is radiodense with patchy lucencies. There is a subtle periosteal reaction* ➔. **(Right)** *Coronal T1-weighted MR shows the medullary cavity is filled with a low-signal mass. The tumor involves a long extent of the bone and does not transgress the cortex.*





## TERMINOLOGY

### Synonyms

- Low-grade central osteosarcoma
- Low-grade intramedullary osteosarcoma

### Definitions

- Neoplasm composed of bland spindle cells and woven bone with limited metastatic potential
  - Histologically similar to surface low-grade osteosarcoma (parosteal osteosarcoma)

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Very uncommon
    - Represents ~ 1% of all osteosarcomas
- Age
  - Develops during 2nd-5th decades of life
  - 50% of patients are in their 20s at diagnosis
- Sex
  - Equal sex distribution

### Site

- Medullary cavity of metaphysis or metaphyseal-diaphyseal region of long bones
  - Femur followed by tibia; uncommon in flat bones

### Presentation

- Pain for months to years prior to diagnosis
- Enlarging palpable mass
- Occasionally can be discovered incidentally

### Treatment

- Surgery alone: Associated with low risk of dissemination

### Prognosis

- Metastatic rate ~ 15%
  - Metastases often develop from tumors that have undergone dedifferentiation

## IMAGING

### Radiographic Findings

- Densely cloud-like and mineralized; some are radiolucent
- Poorly demarcated margins
- May cause bone expansion with little periosteal reaction
- May have soft tissue extension that is relatively small compared to intramedullary component

### MR Findings

- Signal intensity depends on degree of mineralization
  - T1 most commonly low signal
  - T2 heterogeneous when lesion significantly mineralized

### CT Findings

- Sclerotic
- Helpful in delineating extent of bone involvement

## MACROSCOPIC

### General Features

- Hard, gritty, tan-white
- Poorly defined margins
- Cortical destruction and associated soft tissue mass may be present

## MICROSCOPIC

### Histologic Features

- Mild to moderately cellular cytologically bland spindle cell component
  - Neoplastic cells intimately associated with long trabeculae or round islands of woven bone, which may have pagetoid appearance
- Grows with infiltrative pattern
  - Tumor replaces marrow space and surrounds preexisting bony trabeculae that may serve as scaffolding for deposition of tumor bone
- Tumor rarely undergoes dedifferentiation

## ANCILLARY TESTS

### Immunohistochemistry

- Most low-grade intramedullary osteosarcomas stain for MDM2 and CDK4

### Genetic Testing

- *MDM2* amplification can be detected by FISH

## DIFFERENTIAL DIAGNOSIS

### Fibrous Dysplasia

- Nonaggressive radiological features
  - Has ground-glass appearance
- Curvilinear bone deposition
- Lacks infiltrative growth pattern
- In craniofacial skeleton, distinguishing fibrous dysplasia from low-grade osteosarcoma can sometimes be difficult
- Negative for MDM2 and CDK4; has *GNAS* mutation

### Desmoplastic Fibroma

- Broad fascicles of spindle-shaped cells similar to what is seen in well-differentiated osteosarcoma
- Does not contain neoplastic bone
- Usually does not grow with infiltrative growth pattern

### Fibrosarcoma

- Low-grade fibrosarcoma can show infiltrative growth pattern, mimicking well-differentiated osteosarcoma
- Neoplastic bone formation is not present

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Well-differentiated intramedullary osteosarcoma should always be included in differential diagnosis of fibroosseous lesion, especially on small biopsy
  - Histologic features should be correlated with radiographic appearance of tumor

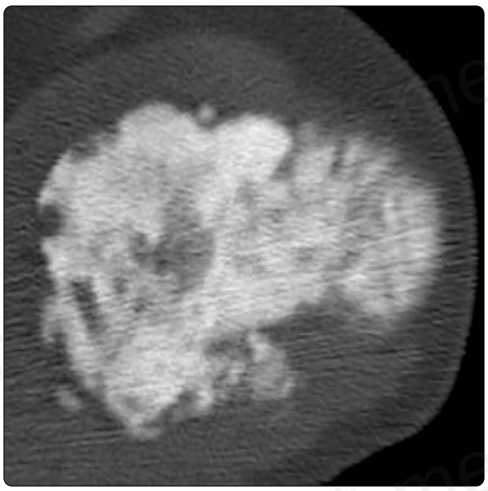
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2. Demicco EG et al: Well-differentiated osteosarcoma of the jaw bones: a clinicopathologic study of 15 cases. Am J Surg Pathol. 34(11):1647-55, 2010

**Large Mineralized Tumor**



**Large Mass Obliterates Bone**



**(Left)** *This well-differentiated osteosarcoma is large and has extended through the cortex and grows along the surface and into the soft tissues. The tumor is radiodense.* **(Right)** *Accompanying axial CT to the radiograph of the humeral tumor shows that the osteosarcoma obliterates the medullary cavity and extends into the soft tissues.*

**Trabeculated Tumor**



**Large Mass**



**(Left)** *In this CT scout image, the tumor fills and expands the proximal tibia. The mass is lucent and has produced a trabecular pattern caused by prominent endosteal ridges. The tumor has eroded the lateral cortex.* **(Right)** *In this accompanying coronal CT, the tumor has soft tissue density and has eroded the lateral cortex of the tibia. There is a large soft tissue component ⇨.*

**Lytic Mass**



**Heterogeneous Mass**



**(Left)** *The tumor is located in the distal talus and appears as a radiolucency. The margins are relatively well defined ⇨ and the cortex of the calcaneus is intact.* **(Right)** *Coronal MR of a calcaneal tumor shows a heterogeneous mass that involves the distal portion of the medullary cavity. Transgression of the cortex is present ⇨.*

### Radiodense Mass

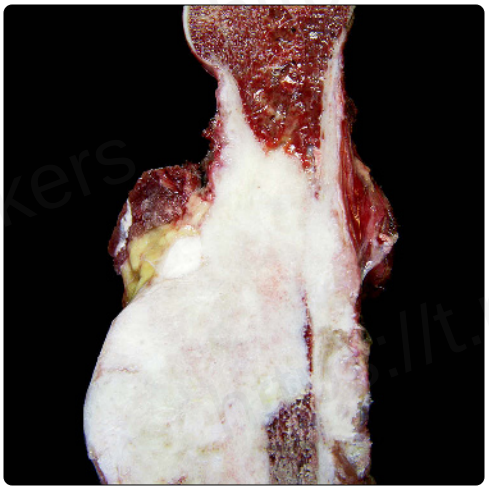


### Tan-White Tumor

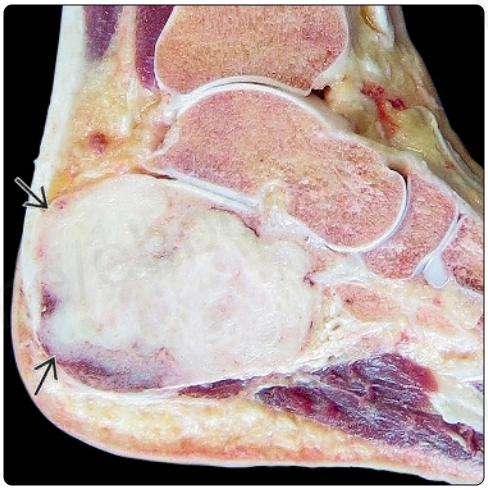


**(Left)** *Lateral radiograph shows an irregular homogeneous radiodense mass that has originated in the medullary cavity of the proximal phalanx of the thumb. The tumor has eroded through the cortex and extends into the soft tissues.* **(Right)** *This is an unusual location for a low-grade osteosarcoma. The tumor arises in the proximal phalanx and is tan-white and hard. The tumor extends into the adjacent soft tissues ⇨.*

### Heavily Mineralized Tumor

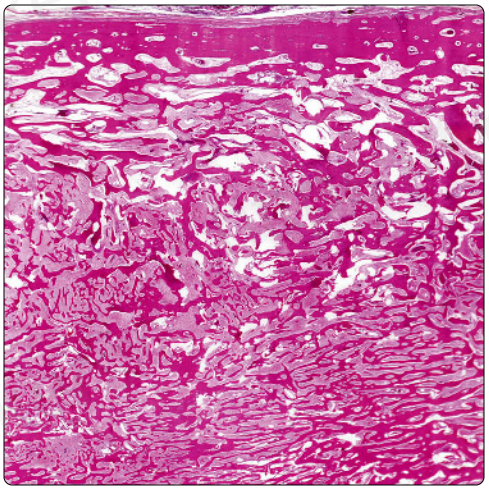


### Fish Flesh-Like Mass

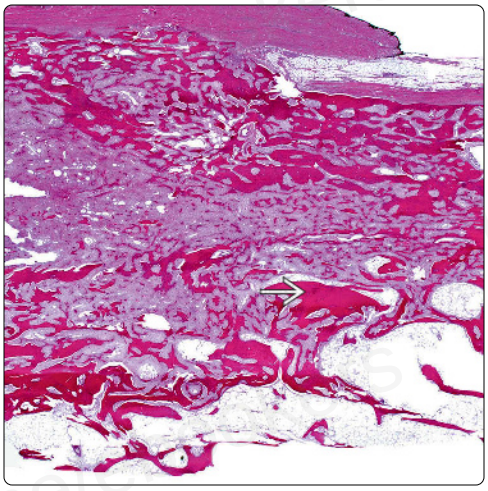


**(Left)** *The osteosarcoma is hard and pearly white. The tumor arises in the medullary cavity and extends through the cortex forming a large soft tissue mass.* **(Right)** *The tumor replaces most of the calcaneus and grows into the soft tissues ⇨. It is firm and fish flesh-like in appearance.*

### Infiltrative Growth Pattern



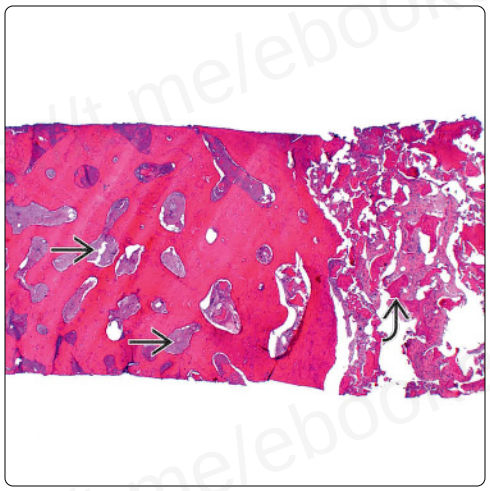
### Permeation of Marrow Space



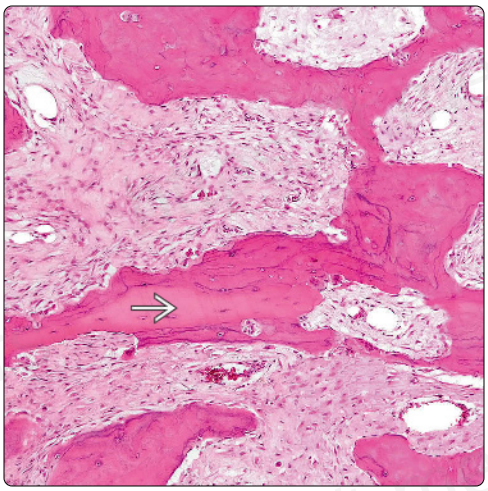
**(Left)** *Low-grade osteosarcoma grows with an infiltrative pattern and surrounds preexisting bony trabeculae. The tumor makes abundant, well-formed, trabecular-type bone that are long and interconnected.* **(Right)** *The osteosarcoma grows with an infiltrative pattern and replaces the fatty marrow and surrounds the preexisting bony trabeculae ⇨. The spindle cell component of the tumor is pale pink.*

**(Left)** *Needle biopsy of an intramedullary low-grade osteosarcoma shows tumor percolating through the haversian systems in the cortex ⇨. The medullary cavity is also filled with the neoplasm that is producing woven bone ⇨.* **(Right)** *Well-differentiated osteosarcoma shows broad seams of osteoid. The intervening spaces are occupied by a spindle cell population. The tumor surrounds the preexisting trabeculae ➡.*

### Needle Biopsy

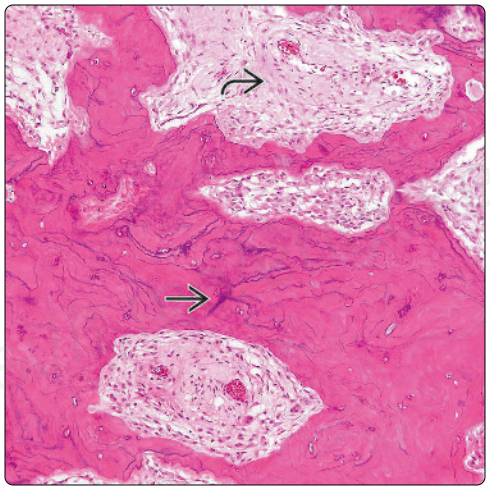


### Trabeculum Surrounded by Tumor

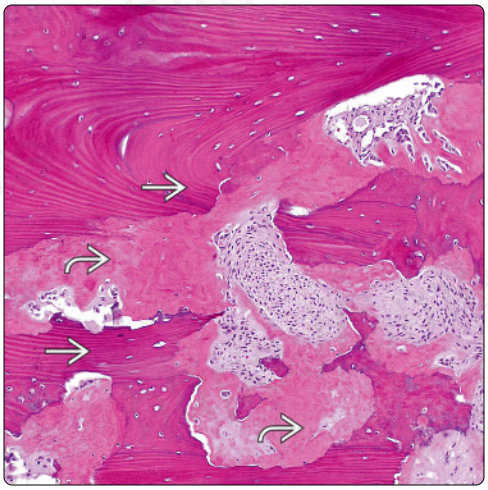


**(Left)** *Well-differentiated intramedullary osteosarcoma with broad interconnected seams of osteoid shows bone with a pagetoid appearance ("mosaic bone") ⇨. Note the low-grade fibroblastic component ⇨. Tumor cells are abutting the neoplastic bone; osteoblasts are not seen.* **(Right)** *The neoplasm grows with an infiltrative pattern within the medullary cavity. The tumor completely surrounds the preexisting trabeculae ➡ and uses them for scaffolding for the deposition of the neoplastic matrix ➡.*

### Pagetoid Pattern

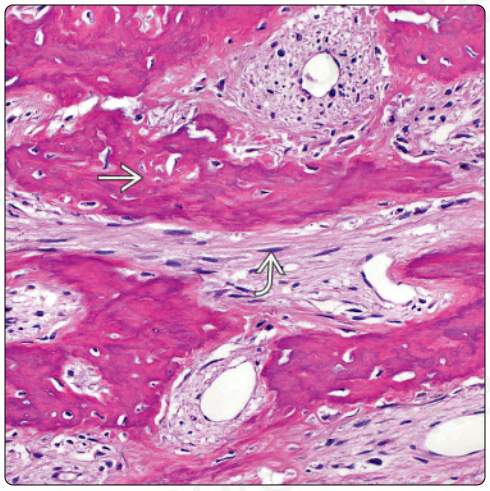


### Permeation of Bone

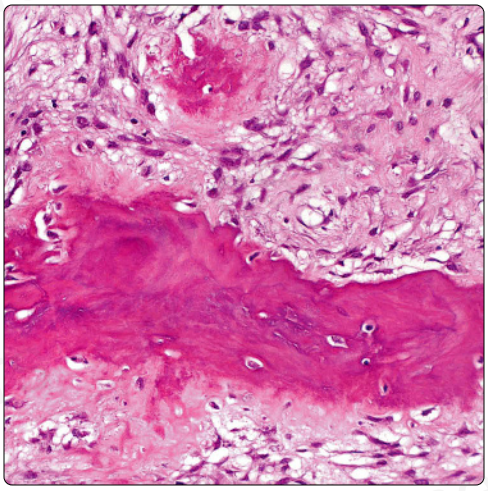


**(Left)** *The neoplastic bone in low-grade intramedullary osteosarcoma is composed of relatively well-formed trabeculae of woven bone ➡. The tumor cells are spindled ➡ and do not demonstrate significant cytologic atypia.* **(Right)** *The tumor cells are arranged in poorly formed fascicles and in a random fashion. Their nuclei contain fine chromatin and are uniform in appearance. They line the bone-forming surfaces of the neoplastic matrix.*

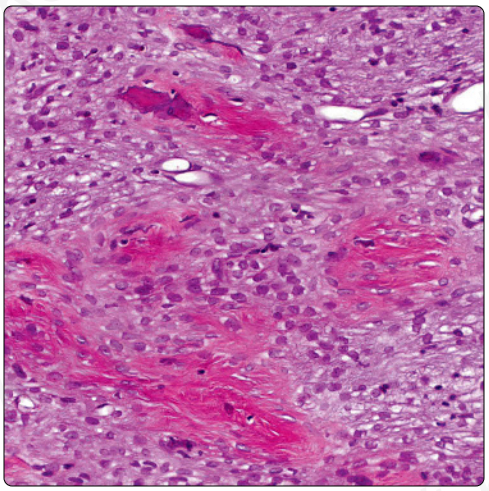
### Neoplastic Woven Bone



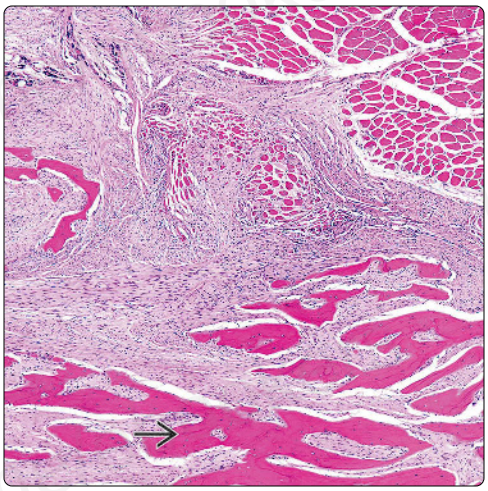
### Tumor Bone and Spindle Cells



### Cellular Tumor

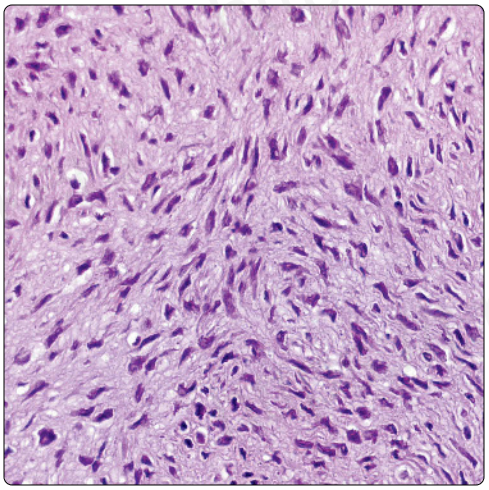


### Periphery of Tumor

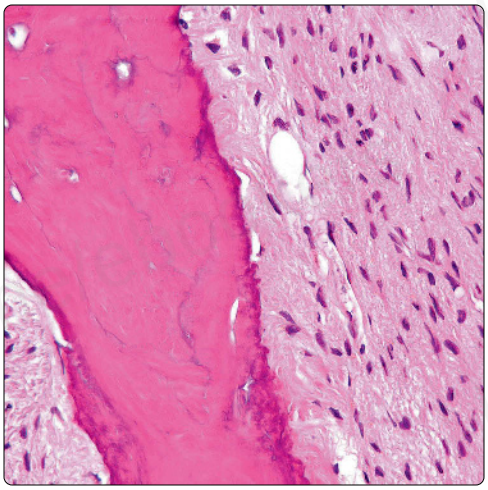


**(Left)** *This low-grade osteosarcoma is hypercellular and the neoplastic cells are ovoid and have pink to clear cytoplasm. Despite cellularity, there are no cytologic atypia or mitotic figures. The neoplastic bone is fibrillar in appearance.* **(Right)** *Well-differentiated intramedullary osteosarcoma shows parallel seams of osteoid ⇨ surrounded by a fibroblastic component. The tumor shows a superficial resemblance to fibrous dysplasia; however, fibrous dysplasia would not infiltrate surrounding soft tissue, as seen in this image.*

### Fascicles of Spindle Cells

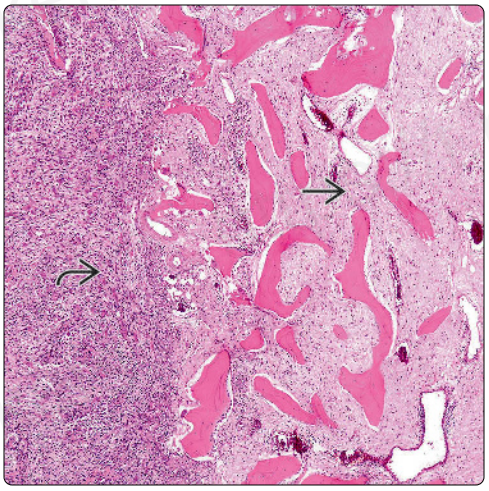


### Tumor Cells and Neoplastic Bone

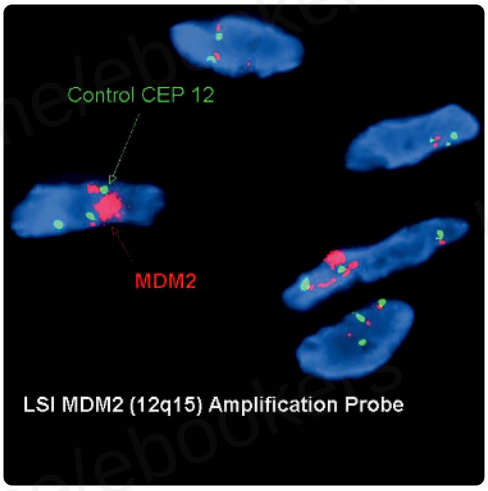


**(Left)** *In this area of a well-differentiated osteosarcoma, the tumor is composed of spindle cells arranged in intersecting fascicles. There is limited cytologic atypia, very little mitotic activity, and no bone is present.* **(Right)** *High-power view of well-differentiated intramedullary osteosarcoma shows a trabecula of bone with spindle-shaped neoplastic cells in close proximity. The neoplastic cells lack atypia.*

### Dedifferentiation



### *MDM2* Amplification




**(Left)** *Well-differentiated intramedullary osteosarcoma with dedifferentiation to a high-grade osteosarcoma is seen. The low-grade component ⇨ shows parallel seams of bone surrounded by a low-grade spindle cell component. The high-grade element ⇨ shows a highly cellular tumor.* **(Right)** *This image of FISH demonstrates amplification of MDM2 that is manifested by the multiple red areas of staining.*

# Parosteal Osteosarcoma

KEY FACTS

## ETIOLOGY/PATHOGENESIS

- Unknown; rarely at site of previous radiation

## CLINICAL ISSUES

- Most common surface osteosarcoma (OSA) (65%); accounts for 5% of OSA
- 80% diagnosed 20-50 years of age; mean: 28 years
- Most common site is posterior femoral cortex in metaphyseal-diaphyseal area of popliteal region
- 5-year survival 91-100%, 10-year survival 80%
- 9-16% undergo dedifferentiation; most metastatic tumors are dedifferentiated

## IMAGING

- Usually uniformly densely mineralized
- Often well delineated with lobulated contour with little or no periosteal reaction
- Extension into medullary cavity present in 20-80% (mean: 50%) of cases

## MACROSCOPIC

- Solid, hard, tan-white; soft tan areas represent fibroblastic component
- Transgresses cortex and invades medullary cavity in 50% of cases

## MICROSCOPIC

- Well-formed trabeculae of woven bone surrounded by mildly to moderately atypical cellular spindle cell proliferation in collagenous stroma
- Dedifferentiated component is high grade and contains pleomorphic spindle cells
- Low-grade chondrosarcomatous foci often present
  - Can mimic osteochondroma

## ANCILLARY TESTS

- MDM2 amplification by FISH and immunohistochemistry

## TOP DIFFERENTIAL DIAGNOSES

- Osteoma and osteochondroma

**Parosteal Osteosarcoma Distal Posterior Femur**



*Parosteal osteosarcoma grows on the posterior cortex of the distal metaphysis of the femur. The tumor is uniformly mineralized and has a lobular contour. There is periosteal reactive bone proximally.*

**Mineralized, Tan-White Mass**



*Parosteal osteosarcoma arises on the posterior femoral cortex. The oval, tan-white mass is well circumscribed and contains central ossification. The tumor is sitting on the surface of the cortex and does not invade the underlying medullary cavity.*

## TERMINOLOGY

### Synonyms

- Juxtacortical well-differentiated osteosarcoma (OSA), surface well-differentiated (low-grade) OSA

### Definitions

- Low-grade OSA that arises on surface of bone

## ETIOLOGY/PATHOGENESIS

### Neoplasm

- Mutation in mesenchymal stem cell producing neoplasm; rarely develops at site of previous radiation

### Cytogenetics

- Ring chromosomes containing 12q13-15

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - 1 per 8 million people; accounts for 5% of all OSAs; most common type of surface OSA, represents 65% of surface OSAs
- Age
  - Peak incidence is during 3rd decade of life; 80% diagnosed between 20-50 years; mean: 28 years
- Sex
  - Predilection for females; M:F = 1:1.3

### Site

- Usually arise on surface of tubular bones; 91% involve metaphysis, 64% limited to metaphysis, 15% metaphyseal and diaphyseal, 8% metaphyseal and epiphyseal, 9% limited to diaphysis
- Most common site is posterior femoral cortex in metaphyseal-diaphyseal area of popliteal region

### Presentation

- Slowly enlarging, firm, palpable mass; pain may be present

### Treatment

- Surgical excision; adjuvant radiation when complete resection not possible; chemotherapy when tumor undergoes dedifferentiation

### Prognosis

- Good: 5-year survival 91-100%, 10-year survival 80%; local recurrence rate 7-50%
- 6% metastasize by 5 years and 11% at 10 years
  - Most tumors that metastasize are usually dedifferentiated; 9-16% undergo dedifferentiation

## IMAGING

### Radiographic Findings

- Generally uniformly densely mineralized; may exhibit radiolucent areas; often well delineated with lobulated contour with variable periosteal reaction
- Appear separate from underlying cortex except for limited area of attachment
  - Radiolucent line separating base of tumor from adjacent cortex present in 58% of cases
- Underlying cortex normal (49%), thickened (29%), or destroyed (21%); extension into medullary cavity present in 20-80% of cases

### MR Findings

- Well-circumscribed mass with mineralized component having low signal intensity on T1WI and T2WI
  - Fibroblastic and cartilaginous areas have increased signal intensity on T1 and T2 sequences; sensitive for identifying intramedullary invasion

### CT Findings

- Well-circumscribed mineralized mass with high signal intensity; unmineralized peripheral component with low-attenuation signal present in 1/3 of cases

### Bone Scan

- Increased uptake on scintigraphy

## MACROSCOPIC

### General Features

- Solid, hard, tan-white; may have gray, firm, glistening hyaline cartilage cap; soft tan areas represent fibroblastic component
- Firmly attached to cortex and tends to grow circumferentially around bone, invades medullary cavity in 50% of cases

### Size

- Usually large (2-30 cm), mean: 9 cm

## MICROSCOPIC

### Histologic Features

- Well-formed, long, woven bone trabeculae with cement lines, surrounded by mild to moderate cellular fascicles of spindle cells
- Spindle cells have elongate nuclei with pointed ends and show low to moderate degrees of cytologic atypia; frequently resembling fibromatosis
- Higher grade foci contain nuclei with coarse chromatin and greater degree of mitotic activity and often arranged in herringbone pattern
- Cartilaginous cap consists of mildly to moderately atypical chondrocytes in hyaline matrix, mimicking osteochondroma

## ANCILLARY TESTS

### Immunohistochemistry

- Neoplastic cells show nuclear staining for MDM2

### In Situ Hybridization

- MDM2 amplification by FISH: More specific and sensitive than immunohistochemistry

## DIFFERENTIAL DIAGNOSIS

### Osteoma

- Cortical-type bone and no spindle cell component

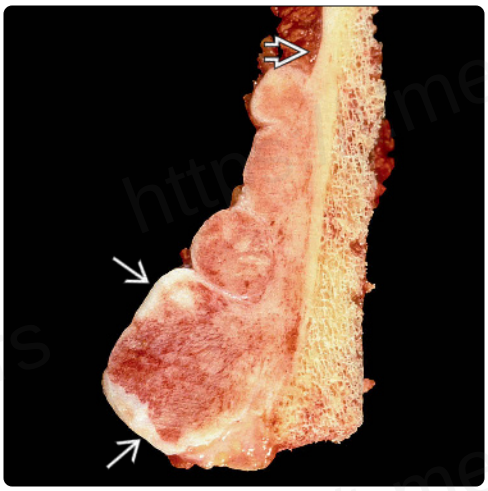
## SELECTED REFERENCES

1. Hang JF et al: Parosteal osteosarcoma. Arch Pathol Lab Med. 138(5):694-9, 2014

**Parosteal Osteosarcoma Distal Femur**



**Solid Mass With Cartilaginous Cap**



**(Left)** *Typical radiographic appearance and location for a parosteal osteosarcoma arising in the distal posterior femur is shown. The tumor is extensively mineralized and the underlying cortex appears to be intact.* **(Right)** *Parosteal osteosarcoma is growing along the surface of the cortex. The pink-tan solid tumor has sharp margins and is focally covered by a white cartilaginous cap. The tumor does not invade the cortex, and subperiosteal reactive bone is present proximally.*

**Tumor Arising From Anterior Femur**



**Parosteal Osteosarcoma of Anterior Femur**

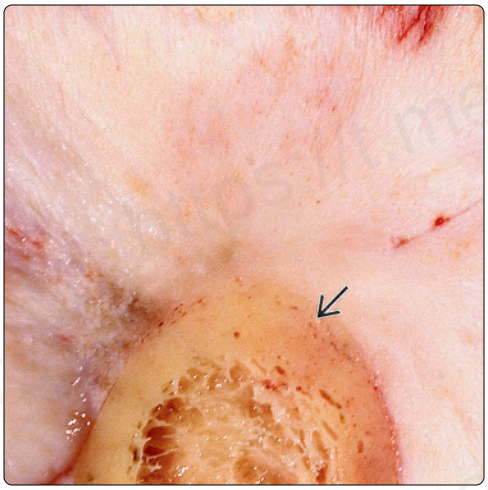


**(Left)** *This parosteal osteosarcoma arises from the anterior surface of the distal femur. The tumor has flocculent mineralizations and does not appear to invade the underlying medullary cavity.* **(Right)** *Corresponding MR shows that the tumor arises from the surface of the bone and is sitting on the underlying cortex. No involvement of the underlying medullary cavity is present.*

**Tan-White Tumor on Surface of Femur**



**Base of Parosteal Osteosarcoma**



**(Left)** *Resected parosteal osteosarcoma is anchored to the surface of the cortex. The tan-white tumor is well circumscribed with a smooth contour. The tumor grows around 1/2 of the circumference of the bone. The underlying cortex is intact and uninvolved.* **(Right)** *Base of parosteal osteosarcoma is firmly attached to the femoral cortex. The firm, tan-white tumor is adherent to the bone with limited subperiosteal reactive bone. The cortex is not invaded.*

Diaphyseal Parosteal Osteosarcoma

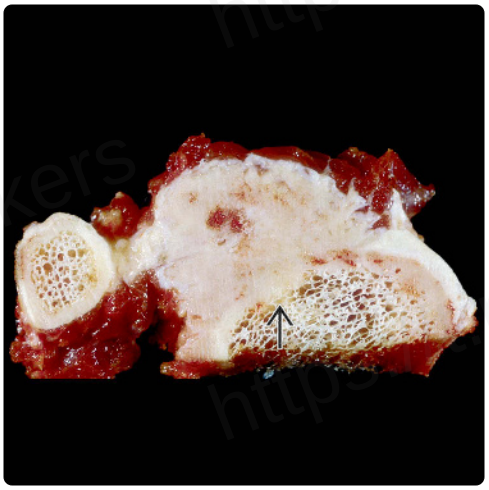


Fibula Invading Medullary Cavity

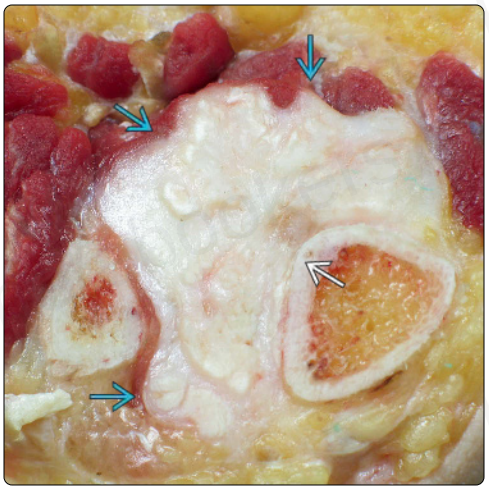


**(Left)** *AP view of the distal femur shows a large partially ossified mass that is adherent to the medial distal cortex. The tumor bulges into the adjacent muscle, and its inferior margin is ill defined and contains components that have a soft tissue radiodensity.* **(Right)** *Parosteal osteosarcoma arising from the fibula is shown. The tumor arises from the surface of the bone and is extensively mineralized. Focally, the tumor has invaded through the cortex and into the medullary cavity.*

Invasion Into Medullary Cavity



Tan-White Mass of Foot

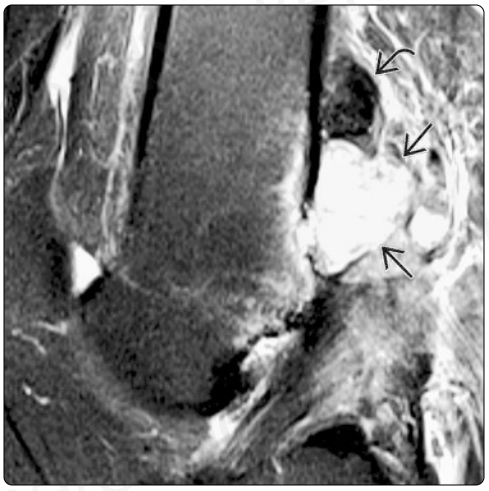


**(Left)** *Cross section of parosteal osteosarcoma grows on the surface of the tibia adjacent to fibula. The tan-white tumor displaces the adjacent muscle, invades the cortex, and extends into the medullary cavity.* **(Right)** *A parosteal osteosarcoma arising from the surface of a small bone of the foot, which is an unusual location, is shown. The tumor is firm, tan-white, and sitting on the underlying cortex, which is intact. The medullary cavity is unremarkable.*

Dedifferentiated Parosteal Osteosarcoma

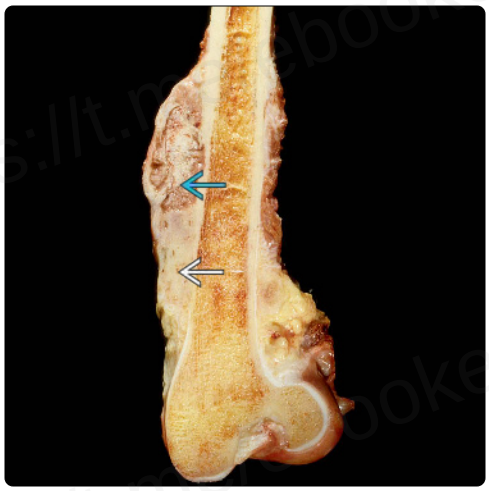


Dedifferentiated Parosteal Osteosarcoma



**(Left)** *Dedifferentiated parosteal osteosarcoma is growing from the distal posterior femur. The well-differentiated ossified element is proximal to the dedifferentiated component, which is not well seen.* **(Right)** *Sagittal T2WI MR of dedifferentiated parosteal osteosarcoma shows the proximal, mineralized, well-differentiated area is hypointense, and the distal dedifferentiated portion is hyperintense. The adjacent endosteal marrow and the posterior soft tissues are edematous.*

### Dedifferentiated Parosteal Osteosarcoma

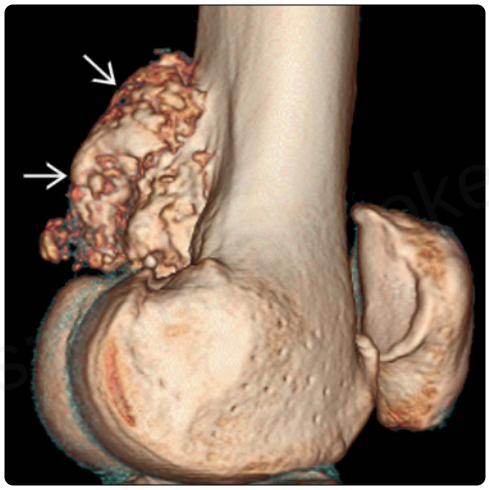


### Dedifferentiated Parosteal Osteosarcoma

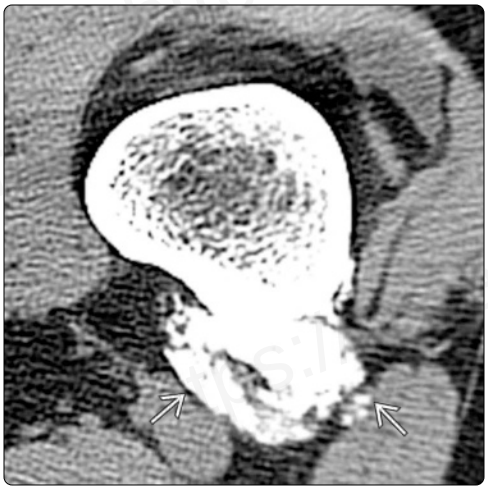


**(Left)** *Dedifferentiated parosteal osteosarcoma arising from the surface of the femur is shown. The tumor has firm and sclerotic areas, but proximally, there is an area that is more fleshy and represents a high-grade transformation (dedifferentiation).* **(Right)** *A higher view of the dedifferentiated component in this parosteal osteosarcoma is shown. The tumor is fleshy, has some central mineralized component, and has focally invaded the underlying cortex.*

### 3D Reconstruction



### Densely Mineralized Tumor

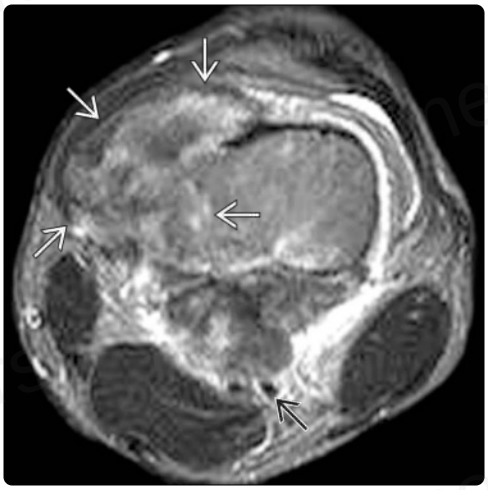


**(Left)** *3D reconstructed image shows a distal femur with an ossified mass that is anchored to the posterior cortex. The tumor has an irregular surface with a crater-like appearance.* **(Right)** *Axial CT scan shows a densely mineralized parosteal osteosarcoma attached to the posterior femoral cortex. The tumor involves ~ 25% of the circumference and bulges into the soft tissues in close proximity to the neurovascular structures. The marrow is not involved.*

### Irregular Contours

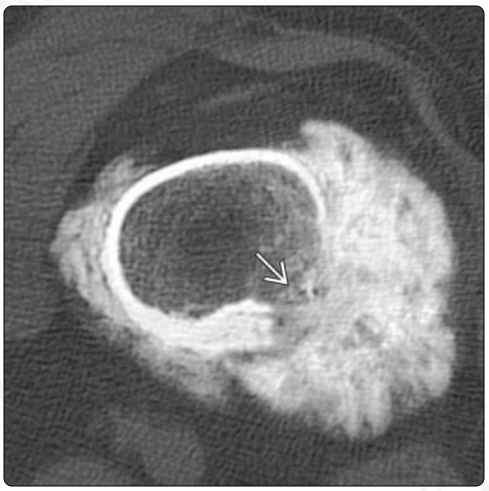


### Invasion of Medullary Cavity

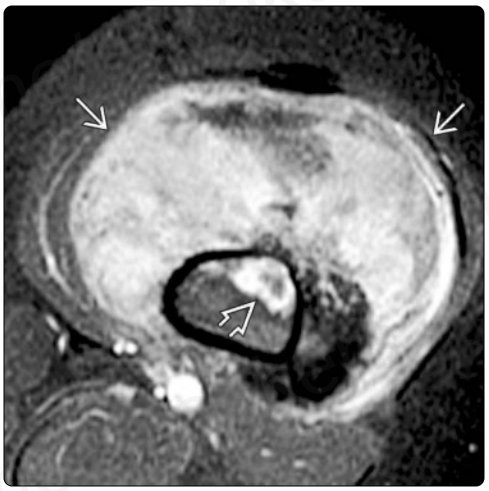


**(Left)** *AP radiograph of the distal femur shows a tumor that is adherent to distal segment of the cortex. The mass has an irregular contour and grows around a portion of the bone. Increased density of metaphysis is medullary or superimposed cortical involvement.* **(Right)** *Axial T2WI MR shows a surface-based heterogeneous mass of the distal medial femur that invades adjacent marrow and displaces the neurovascular bundle. Hyperintense areas represent soft tissue edema.*

### Near Circumferential Involvement



### Invasion of Medullary Cavity

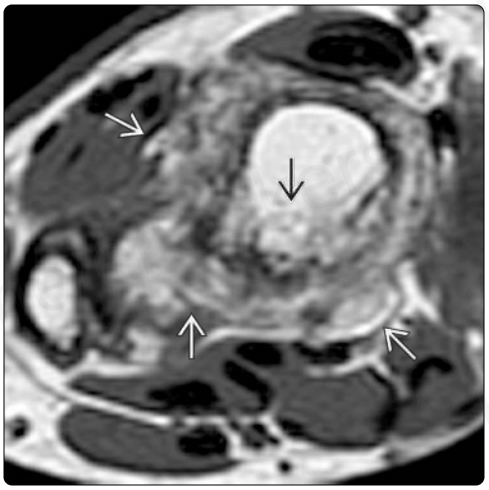


**(Left)** *Parosteal osteosarcoma with near-circumferential neoplastic bone formation grows on the surface of the distal femur. Note the cortical thickening posteriorly with adjacent marrow involvement medially* ➡. **(Right)** *A large, near-circumferential parosteal osteosarcoma is shown with a hyperintense, well-circumscribed component anteriorly* ➡. *Hypointense, dark signal posteromedially represents an ossified portion of the tumor. The mass invades into the marrow cavity anteriorly* ➡.

### Parosteal Osteosarcoma of Radius



### Circumferential Involvement

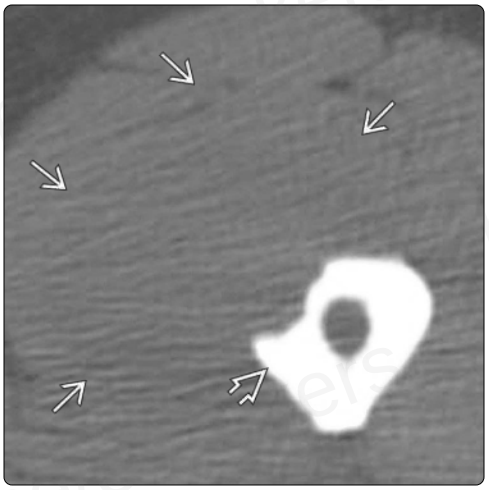


**(Left)** *AP view of the distal radius shows a dense, mineralized lesion involving the distal radial metadiaphysis. The tumor involves the bone circumferentially. Note the pressure erosion on the adjacent ulna* ⇨. **(Right)** *Axial T1WI MR of the radius shows a circumferential, heterogeneous mass. The tumor grows around the bone in a circumferential fashion* ➡, *has an irregular surface, destroys the volar cortex, and invades into the medullary cavity* ⇨.

### Faintly Mineralized Tumor



### Large Parosteal Osteosarcoma



**(Left)** *A subtle soft tissue mass* ➡ *produces a saucerization defect* ⇨ *along the anterior femoral diaphyseal cortex. The tumor has small, faint areas of mineralization scattered throughout. Periosteal reaction is not present.* **(Right)** *Axial CT shows a soft tissue mass* ➡ *isodense to muscle located anteromedial to the femur and causing pressure erosion of the cortex. Note the adjacent cortical thickening posteromedially* ➡. *The medullary cavity is not involved.*

**Mass of Proximal Femur**



**Ossified Tumor**



**(Left)** *Parosteal osteosarcoma with an ossified lobulated mass along the subtrochanteric proximal medial femur is shown. Note the deformity of the femoral neck due to periosteal new bone formation. The lesser trochanter is involved by the mass.* **(Right)** *Axial CT scan shows an ossified parosteal osteosarcoma growing along the posteromedial cortex. The tumor scallops the cortical surface. The margins with the soft tissue are well defined, and the endosteal cortex and marrow cavity are intact.*

**Prominent Cartilage Cap**

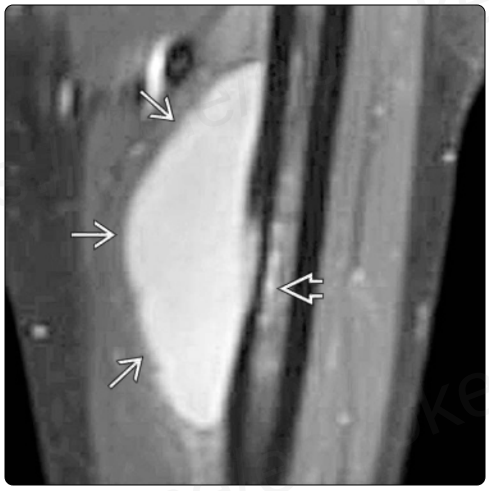


**Cartilage Cap**

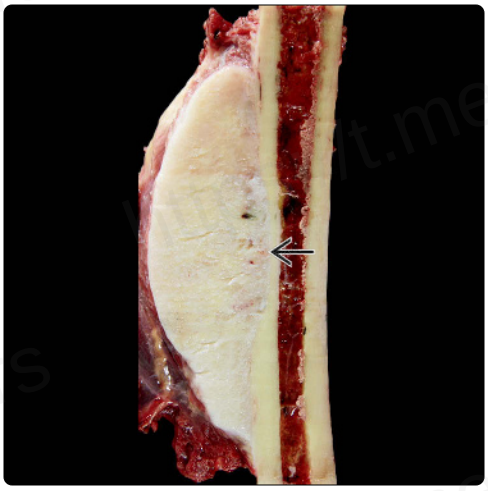


**(Left)** *Coronal T2WI MR shows a hypointense mass adhering to medial proximal femoral cortex. A hyperintense halo represents cartilage capping the ossified mass.* **(Right)** *Parosteal osteosarcoma arises on the proximal femoral cortex and involves the region of the lesser trochanter. A portion of the well-circumscribed tumor is covered by a cap of white neoplastic cartilage. The tan-white tumor is well demarcated, and the underlying cortex is thickened.*

**Diaphyseal Tumor**



**Diaphyseal Tumor**



**(Left)** *A uniform, hyperintense mass abuts the femoral diaphysis with destruction of the outer cortex. The mass has a smooth, sharp margin. Minimal marrow edema is seen in the adjacent endosteal marrow.* **(Right)** *Parosteal osteosarcoma arises from the diaphysis of the femur. The tan-white tumor is well delineated from the adjacent skeletal muscle and has a smooth contour. The tumor erodes the outer layer of the cortex but does not invade into the medullary cavity.*

### Tumor of Mandible

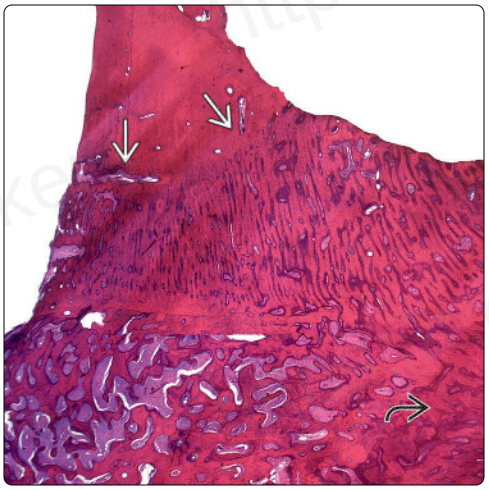


### Dense Tumor of Mandible

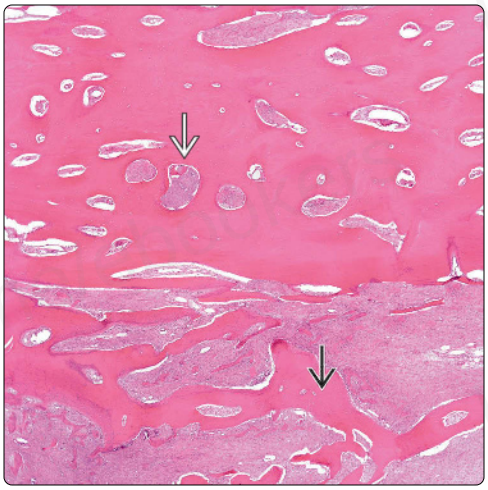


**(Left)** *3D coronal reconstructed CT shows an ossified mass projecting from the inferior margin of the body of the mandible. The small tumor is polypoid in shape and has a well-circumscribed margin.* **(Right)** *Uniformly dense parosteal osteosarcoma ➡ is contiguous with the body of the mandible. The tumor is well circumscribed. The mandibular canal is seen superior to the tumor.*

### Abundant Bone Formation

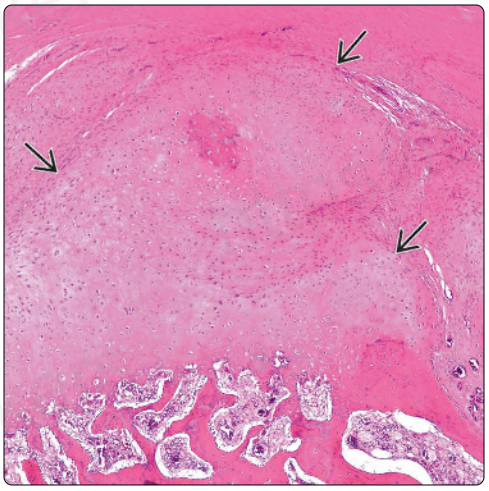


### Permeative Growth Pattern

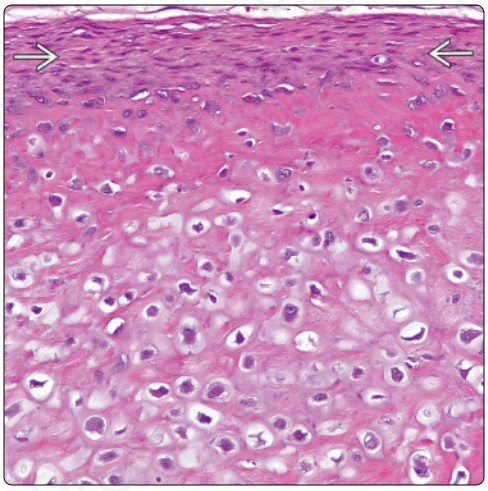


**(Left)** *Parosteal osteosarcoma is attached to the cortex of the mandible ➡. The tumor contains abundant bone deposited in streamers, which focally coalesce into sheet-like aggregates ⇨. The tumor does not invade the cortex.* **(Right)** *Cortex and medullary cavity is shown beneath an invasive parosteal osteosarcoma. The tumor permeates haversian systems ➡ and infiltrates into the medullary cavity where it replaces the fatty marrow and encases preexisting trabecular bone ⇨.*

### Nodular Hyaline Cartilaginous Cap

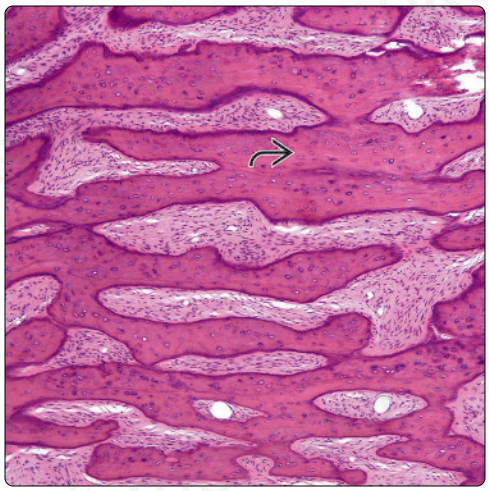


### Cellular Cartilaginous Cap

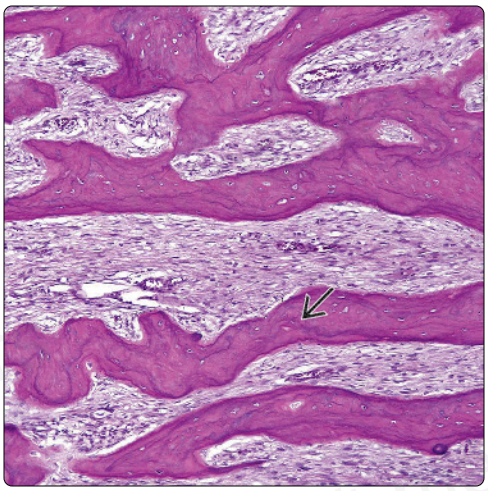


**(Left)** *Nodular hyaline cartilaginous cap ⇨ of parosteal osteosarcoma is covered by a layer of fibrous tissue. Moderately cellular neoplastic cartilage undergoes enchondral ossification forming bony trabeculae surrounded by loose connective tissue.* **(Right)** *The surface of the cartilaginous cap of parosteal osteosarcoma is covered by a cellular neoplastic fibroblastic component ➡. Chondrosarcomatous element is moderately cellular; chondrocytes are atypical.*

### Streamers of Bone

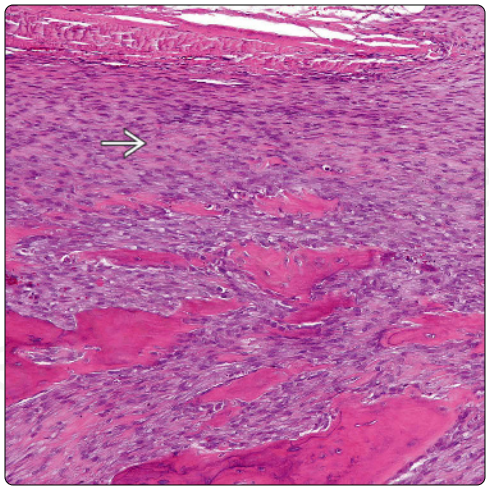


### Bone With Cement Lines

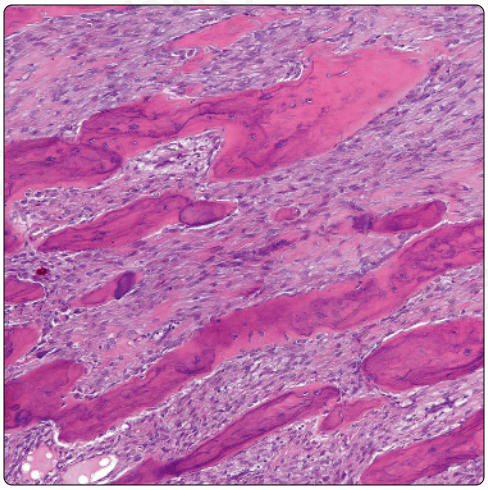


**(Left)** *Streamers of tumor bone are characteristic of parosteal osteosarcoma. The bone is trabecular in pattern and woven in architecture. Fascicles of moderately cellular spindle cells fill the intertrabecular spaces and cover the surfaces of the neoplastic bone.* **(Right)** *Spindle cells arranged in cellular fascicles cover the surfaces of long trabeculae of neoplastic bone, typical of parosteal osteosarcoma. The tumor bone contains numerous cement lines that mimic Paget disease.*

### Surface of Parosteal Osteosarcoma

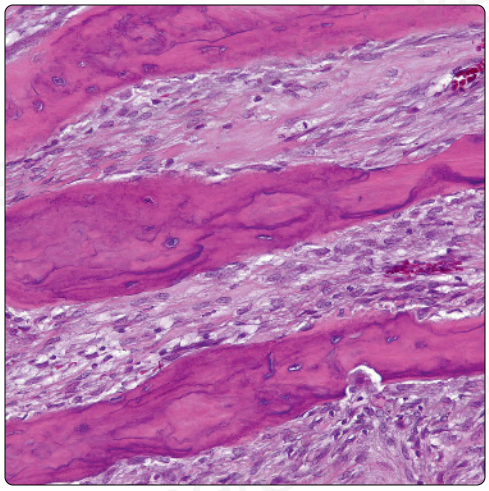


### Parallel Arrangement of Bone

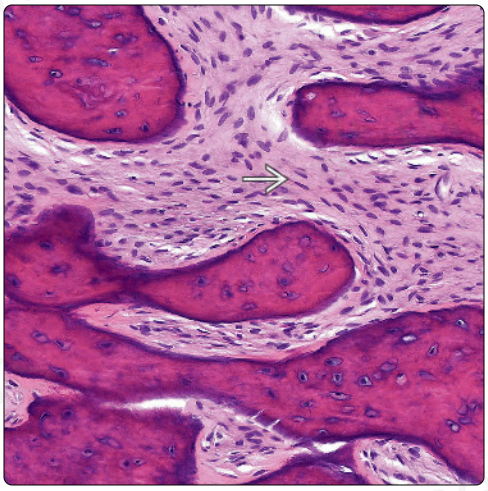


**(Left)** *Surface of parosteal osteosarcoma is composed of a fibroblastic component that resembles fibromatosis or low-grade fibrosarcoma. Neoplastic woven bone appears to arise from fascicles of spindle cells, which are uniform in appearance and demonstrate limited cytologic atypia.* **(Right)** *Neoplastic bone trabeculae in parosteal osteosarcoma are arranged in parallel. The woven bone trabeculae are encompassed by neoplastic spindle cells that resemble those of fibromatosis.*

### Woven Bone

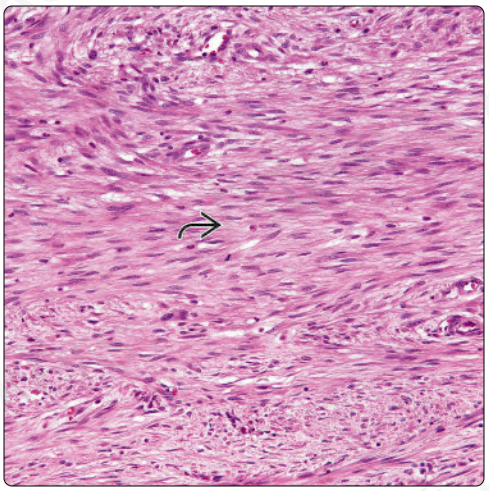


### Bland Spindle-Shaped Cells

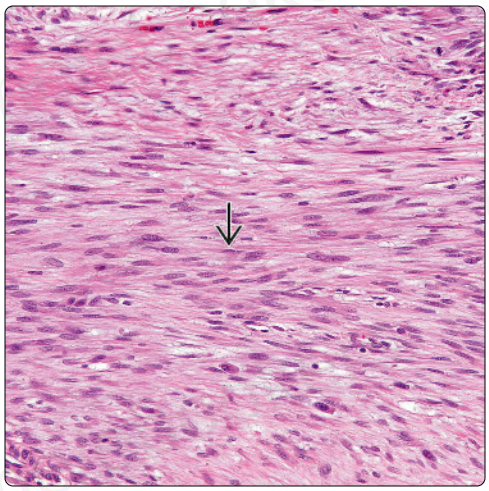


**(Left)** *Neoplastic trabeculae of bone in parosteal osteosarcoma are woven in pattern, contain many cement lines, and are surrounded by fascicles of moderately cellular spindle cells. The spindle cells have elongate nuclei with fine chromatin.* **(Right)** *The fascicles of spindle cells in parosteal osteosarcoma are intimately related to the surfaces of tumor bone. The cells are uniform in appearance and do not demonstrate significant cytologic atypia; there are few mitotic figures.*

Fibroblastic Component

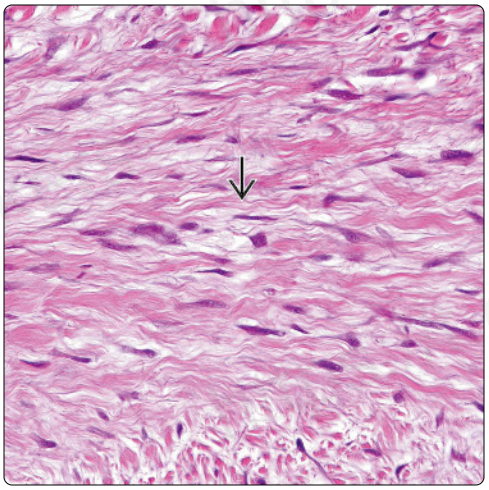


Uniform Spindle-Shaped Cells

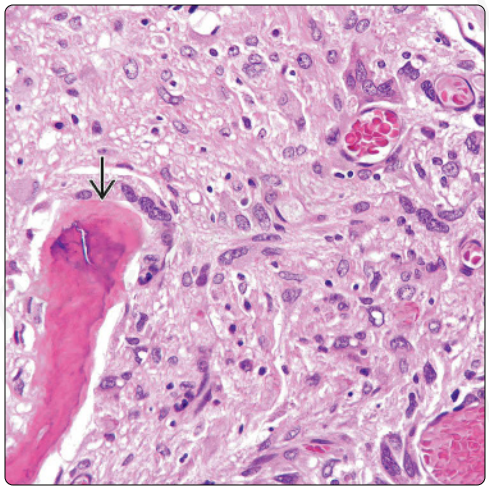


**(Left)** *Fibroblastic component of parosteal osteosarcoma can sometimes account for much of the tumor. Spindle cells are arranged in moderately cellular broad sweeping fascicles ⇨ that can resemble fibromatosis or low-grade fibrosarcoma, depending on degree of cytologic atypia and mitotic activity.* **(Right)** *Spindle cells in the fibroblastic component of parosteal osteosarcoma are uniform and have elongate nuclei with tapered ends ⇨. Cytoplasm is eosinophilic and indistinct.*

Bland Spindle-Shaped Cells



Dedifferentiated Parosteal Osteosarcoma

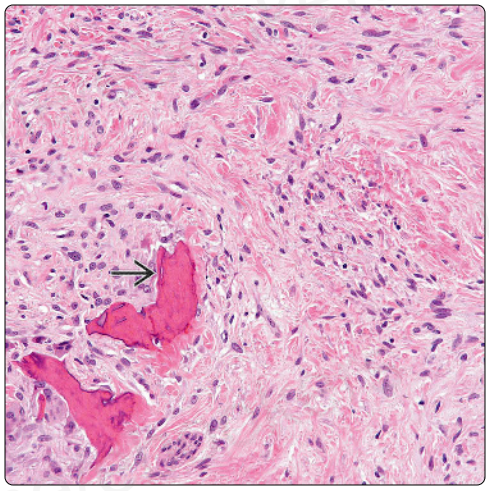


**(Left)** *Fibroblastic spindle cells in parosteal osteosarcoma show no cytologic atypia and are surrounded by prominent bundles of collagen ⇨. This pattern can closely resemble fibromatosis in appearance.* **(Right)** *Well-differentiated component of dedifferentiated parosteal osteosarcoma shows that the woven bone of the low-grade component ⇨ is surrounded by severely atypical spindle and polyhedral cells of dedifferentiated element. In other areas, the atypical cells grow in sheets and fascicles.*

Metastatic Parosteal Osteosarcoma



Metastatic Parosteal Osteosarcoma



**(Left)** *Parosteal osteosarcoma metastasized to the lung is shown. This metastatic, low-grade tumor is well delineated and contains a small amount of neoplastic trabecular bone ⇨.* **(Right)** *In this metastatic parosteal osteosarcoma to the lung, well-formed neoplastic bone ⇨ is surrounded by mildly atypical spindle cells demonstrating very few mitotic figures associated with abundant collagen. Although most cases that metastasize are dedifferentiated, this is low grade.*

# Periosteal Osteosarcoma

KEY FACTS

## TERMINOLOGY

- Intermediate-grade chondroblastic osteosarcoma that arises on surface of bone

## CLINICAL ISSUES

- Uncommon variant of osteosarcoma
- Typically develops in 2nd and early 3rd decades of life
- Usually arises on surface of long bones: Femur (44%), tibia (39%)
- Commonly develops in region of diaphysis (66%) followed by metaphysis
- Patients present with enlarging, firm, fixed mass
- Optimal treatment is limb salvage surgical resection with negative margins
- Use of chemotherapy is controversial
- Prognosis is good with local recurrence rate of ~ 7% and overall survival of 85%

## IMAGING

- Lucent, fusiform surface mass with broad base of attachment
- May have intratumoral linear reactive bone radiating from base
- Well demarcated from soft tissue, infrequently invades bone
- Cartilaginous component bright on T2

## MACROSCOPIC

- Oblong, solid, pearly white cartilaginous mass

## MICROSCOPIC

- Sarcoma with abundant neoplastic cartilage matrix and foci of tumor bone formation

## TOP DIFFERENTIAL DIAGNOSES

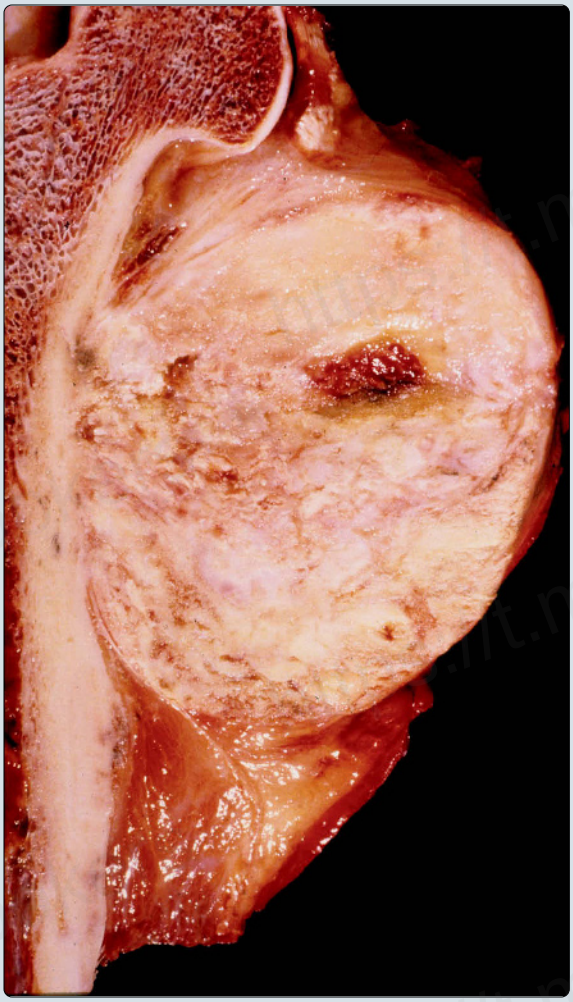
- Bizarre parosteal osteochondromatous proliferation
- Osteochondroma
- Parosteal osteosarcoma

**Large Mineralized Mass**



*Plain radiograph shows periosteal osteosarcoma that is broadly attached to the cortex and has subtle fluffy and linear calcifications. The cortex proximal to the tumor is thickened by reactive bone.*

**Large Tumor Anchored to Cortex**



*Periosteal osteosarcoma is shown arising on the surface of the proximal femur. The oval, tan-white, nodular tumor is well circumscribed and delineated by the periosteum. The tumor scallops the outer cortex.*

## TERMINOLOGY

### Synonyms

- Juxtacortical chondroblastic osteosarcoma

### Definitions

- Intermediate-grade chondroblastic osteosarcoma originating on surface of bone

## ETIOLOGY/PATHOGENESIS

### Neoplastic

- Results from mutation in mesenchymal stem cells; no specific genetic abnormality

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Uncommon tumor; incidence rate is unknown
  - Accounts for 1-2% of all osteosarcoma
  - Represents 25% of surface osteosarcoma
- Age
  - Commonly develops in 2nd and early 3rd decades of life
    - Broad age range of 1-72 years; average: 22 years
- Sex
  - Slight female predominance
    - M:F = 1.0:1.2

### Site

- Most common bones are femur (44%) and tibia (39%) followed by ulna and humerus (5-10%)
- Surface of diaphysis (66-92%) followed by metaphysis
  - Middistal femoral diaphysis and proximal tibial diaphysis

### Presentation

- Slow or rapidly growing, fixed palpable mass
- Pain, swelling

### Treatment

- Limb salvage surgical resection with negative margins
- No consensus regarding systemic chemotherapy
- Adjuvant radiation used in cases of incomplete excision

### Prognosis

- Local recurrence rate: ~ 7%
- Overall survival: 85%; 5-year survival 83-89%
- Recent studies utilizing chemotherapy show benefit
- Recurrence or death occur within 36 months of diagnosis

## IMAGING

### Radiographic Findings

- Lucent fusiform mass with hair on end pattern radiating from cortex and extrinsic scalloping
- Solid periosteal cortical thickening or Codman triangle
- Cartilaginous produces spiculated pattern of calcification

### MR Findings

- Nonmineralized portions isointense to muscle on T1 and heterogeneous high signal intensity on T2
  - Mineralized areas have signal void
- Well-circumscribed margins
- Cortical thickening and scalloping

### CT Findings

- Nonmineralized component has attenuation signal lower than muscle
- Mineralized component shows high signal attenuation
- Well-circumscribed margins
- Cortical thickening and scalloping

### Bone Scan

- Homogeneous marked uptake on scintigraphy

## MACROSCOPIC

### General Features

- Firm, focally gritty, lobulated pearly white mass
- Well-circumscribed pushing margins
- Anchored along broad base to underlying cortex
- Invasion into medullary canal present in 2-25%
  - Medullary invasion is focal
  - If medullary invasion is extensive then difficult to distinguish from conventional osteosarcoma
- Grows along circumference of bone
  - Covers 50-55% of circumference; can encircle bone

### Size

- Large at diagnosis, 1-28 cm; average: 10 cm

## MICROSCOPIC

### Histologic Features

- Neoplastic hyaline/myxoid cartilage predominates
- Moderate-to-severe cytologic atypia and mitotic activity
- Tumor bone coarse, lace-like, and merges with or surrounded by cartilage
- Fascicles of malignant spindle cells may be present

## DIFFERENTIAL DIAGNOSIS

### Bizarre Parosteal Osteochondromatous Proliferation

- Reactive fibrous tissue overlies cellular cartilage cap, which undergoes enchondral ossification

### Osteochondroma

- Cartilage cap hypocellular and banal
- Medullary cavity continuous with center of lesion

### Juxtacortical Chondroma

- Cytologically benign-appearing cartilage and no neoplastic bone

### Parosteal Osteosarcoma

- Contains low-grade cartilage and neoplastic bone

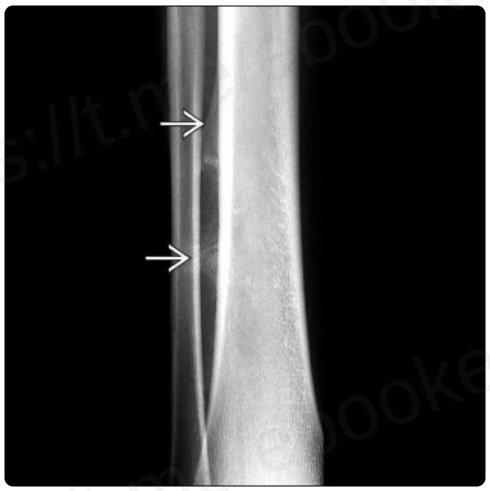
### High-Grade Surface Osteosarcoma

- Composed of high-grade, bone-forming sarcoma

## SELECTED REFERENCES

1. Rose PS et al: Periosteal osteosarcoma: long-term outcome and risk of late recurrence. Clin Orthop Relat Res. 453:314-7, 2006
2. Grimer RJ et al: Periosteal osteosarcoma--a European review of outcome. Eur J Cancer. 41(18):2806-11, 2005

### Surface Mineralized Tumor

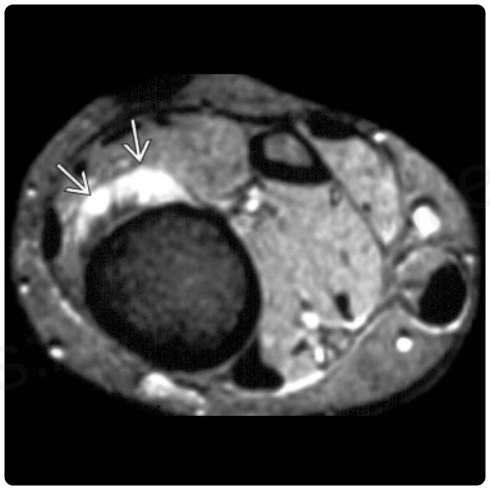


### Surface Tumor With Mineralization



**(Left)** *Plain radiograph of the distal leg shows a lytic mass on the surface associated with periosteal bone formation ➔ arising from the anterolateral cortex of the tibia. There is no evidence of cortical destruction or marrow abnormality.* **(Right)** *CT scan through the distal leg shows linear periosteal bone ⇨ extending through a periosteal osteosarcoma. The tumor is of mostly very low attenuation ➔, consistent with the high water content typical of neoplastic cartilage.*

### T2-Bright Tumor



### Large Fusiform Mass



**(Left)** *T2-weighted MR shows a periosteal osteosarcoma of the tibia. The mass has a broad base of attachment to the tibia and is very bright, suggesting a high water content. The nodular configuration ➔ of the T2-bright formations suggests the presence of cartilage.* **(Right)** *A large tan periosteal osteosarcoma has a broad attachment to the underlying cortex. The tumor is bordered proximally and distally by periosteal reactive bone ⇨. The medullary cavity is not invaded.*

### Juxtacortical Lytic Mass

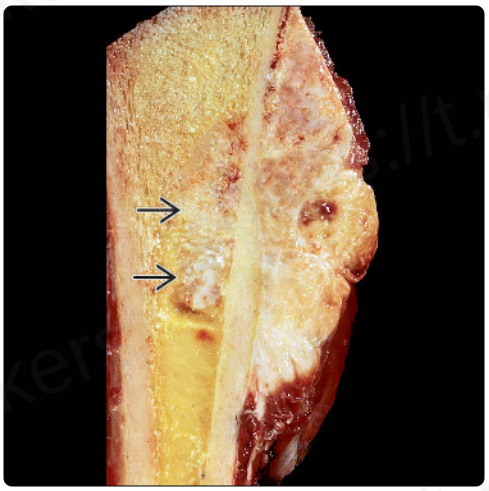


### Cartilage in Periosteal Osteosarcoma

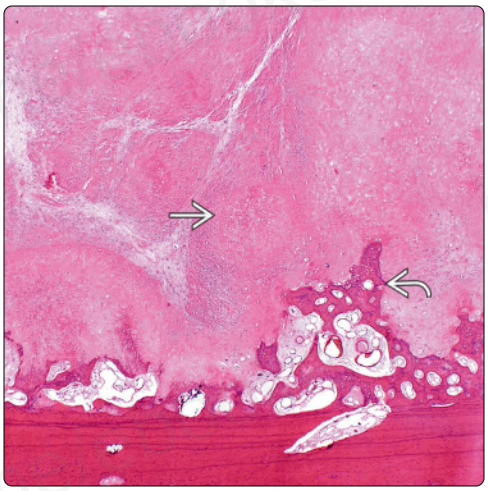


**(Left)** *A periosteal osteosarcoma arising from the mid tibia is very subtle and produces mild cortical irregularity ⇨ mainly visible as a small focus of mineralized periosteal elevation (Codman triangle) ⇨. The underlying bone appears normal.* **(Right)** *Periosteal osteosarcoma has a multinodular appearance ➔ suggestive of hyaline cartilage. A smaller focus has more uniformly high signal intensity ⇨ suggesting a more conglomerate formation of cartilage or another tissue type.*

### Infiltrating Medullary Cavity

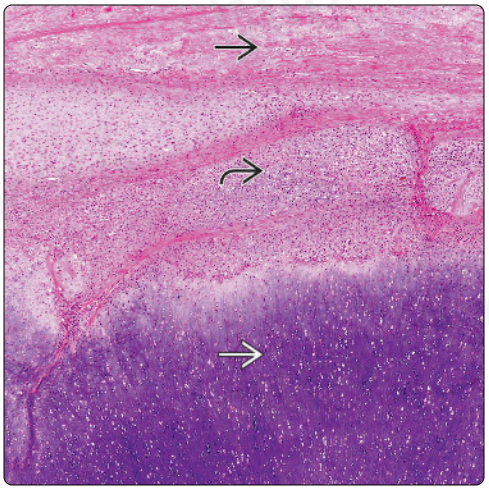


### Nodular Mass With Reactive Bone

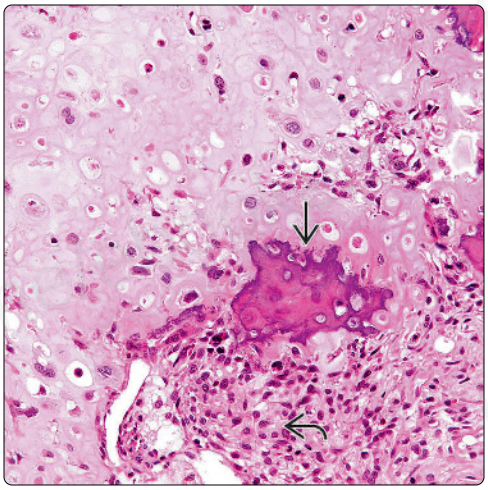


**(Left)** *The periosteal osteosarcoma is based on the surface of the cortex and is tan-white and glistening. The tumor focally infiltrates into the medullary cavity and abuts the marrow fat.* **(Right)** *A large periosteal osteosarcoma is anchored to the surface of the adjacent cortex. The nodular tumor has reactive woven bone extending into the mass.*

### Periphery of Periosteal Osteosarcoma

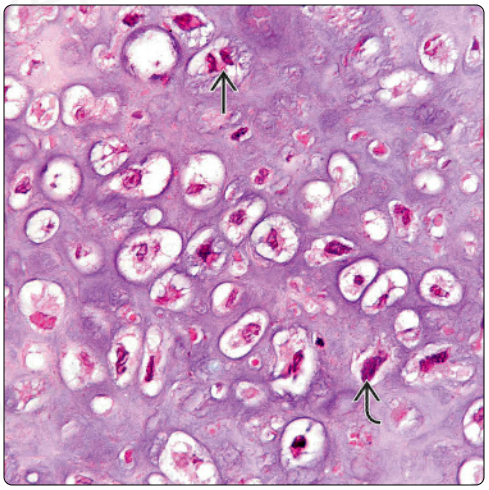


### Periosteal Osteosarcoma Tumor Bone

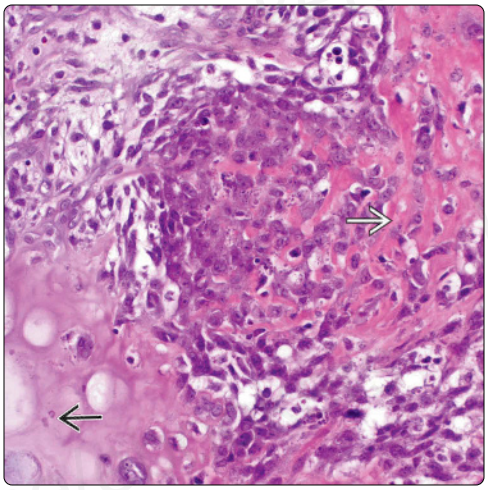


**(Left)** *Periphery of periosteal osteosarcoma is delineated by a layer of fibrous tissue. The peripheral nodules of tumor are the most cellular with limited osteocartilaginous matrix. Deeper portion of tumor contains abundant hyaline matrix.* **(Right)** *Periosteal osteosarcoma is composed of pale pink-blue neoplastic hyaline cartilage, which merges with irregular purple neoplastic bone. Inferior aspect of the bone abuts proliferating cytologically malignant cells with hyperchromatic nuclei.*

### Cartilage of Periosteal Osteosarcoma



### Neoplastic Bone



**(Left)** *Neoplastic cartilage in periosteal osteosarcoma is hyaline, hypercellular, and the tumor cells are enlarged with irregular hyperchromatic nuclei. Note the presence of binucleate cells.* **(Right)** *Coarse, lace-like neoplastic bone is surrounded by cytologically malignant cells in this periosteal osteosarcoma. Adjacent neoplastic hyaline cartilage is less cellular and atypical.*

# High-Grade Surface Osteosarcoma

KEY FACTS

## TERMINOLOGY

- High-grade osteosarcoma that arises on external surface of bone

## CLINICAL ISSUES

- Presents as painful, firm, enlarging mass in adolescents & young adults
- Typically arises on surface of long tubular bones
  - Femur & tibia most frequently affected
- Treated with surgery & chemotherapy like conventional osteosarcoma

## IMAGING

- Oblong or oval mass originating from external cortical surface
  - Has broad site of attachment to underlying cortex
  - Grows circumferentially around bone
  - May transgress cortex & involve medullary cavity
- Extent of tumor best visualized on MR

## MACROSCOPIC

- Large, ovoid, solid, tan-white mass that may be hard & rubbery
- Firmly attached to cortex along large surface area
- Can extend into medullary cavity

## MICROSCOPIC

- High-grade sarcoma in which tumor (TM) cells make neoplastic bone
- Chondrosarcomatous & fibrosarcomatous areas may be present

## TOP DIFFERENTIAL DIAGNOSES

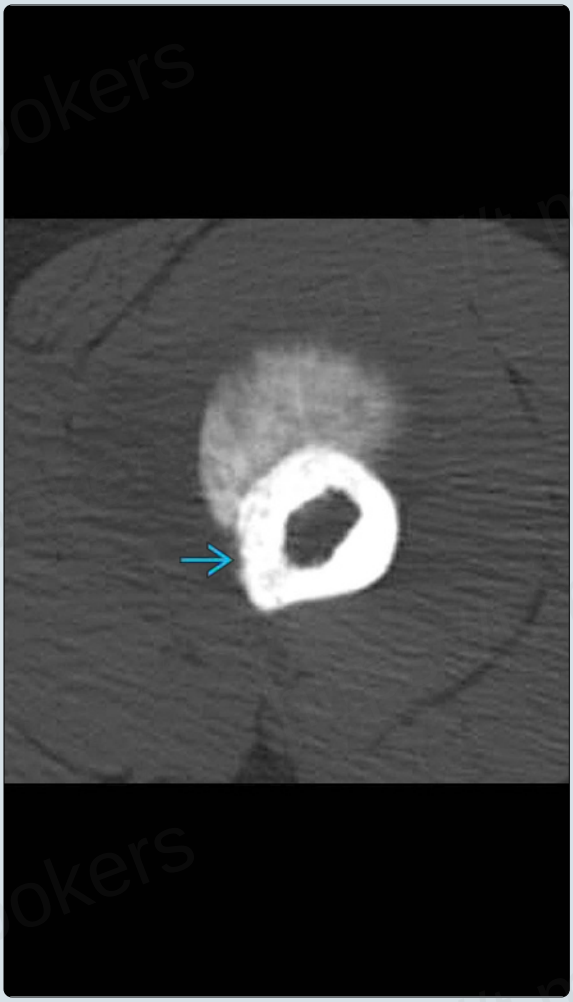
- Osteoma
- Parosteal osteosarcoma
- Periosteal osteosarcoma

**Surface Osteosarcoma**



*Gross image of a resected femur shows an oblong tumor that arises in the midshaft. The tumor originates on the external surface of the cortex and has a broad-based attachment to the bone.*

**Surface Osteosarcoma**



*High-grade osteosarcoma arising on the surface of the femur is shown. The sarcoma shows extensive intratumoral mineralization and appears to involve the cortex of the underlying bone ⇨, but no involvement of the medullary cavity is identified.*

## TERMINOLOGY

### Synonyms

- High-grade juxtacortical osteosarcoma

### Definitions

- High-grade osteosarcoma that arises on external surface of bone

## ETIOLOGY/PATHOGENESIS

### Neoplastic Proliferation

- Likely caused by genetic mutations

## CLINICAL ISSUES

### Epidemiology

- Age
  - Broad age range (8-70 years); 75% of patients in 2nd or 3rd decade of life
- Sex
  - M > F; M:F = 2.2:1

### Site

- External surface of cortex
- Mid portion of diaphysis (62%) followed by diaphyseal-metaphyseal region of long bones; femur > tibia > radius > humerus; rare in distal extremities & flat bones

### Presentation

- Swelling, pain, enlarging fixed mass

### Treatment

- Limb salvage with wide surgical excision; adjuvant chemotherapy; radiation therapy in selected patients

### Prognosis

- Prognosis similar to that of conventional osteosarcoma; 5-year survival rate = 70-80% when treated with complete excision & systemic therapy

## IMAGING

### Radiographic Findings

- Oblong or oval mass originating from external cortical surface; long axis of tumor (TM) parallels direction of host bone; broad base of attachment to underlying bone
- Tends to grow in circumferential fashion
- Degree mineralization & distribution mineralization vary; most TMs contain fluffy to dense radiodensities; areas of mineralization may be spiculated in appearance or resemble calcified cartilage; base of TM most radiodense
- Cortical destruction & thickening often present; focal extension into medullary cavity occurs in ~ 28%; periosteal reaction infrequent
- Margin with soft tissue usually irregular & ill defined

### MR Findings

- Large, oval, heterogeneous mass; variable signal intensity on T1- & T2-weighted images; facilitates identification of cartilage, which may be scattered throughout mass; good modality to demonstrate intramedullary involvement

### CT Findings

- Large, oval mass that has heterogeneous density; mineralized areas have high density similar to bone; cartilaginous & fibroblastic components have densities similar to soft tissue; helps determine anatomic extent of TM

### Bone Scan

- Marked radionucleotide uptake

### PET Scan

- Avid uptake on 18F-FDG PET

## MACROSCOPIC

### General Features

- Large, oval &/or elongated, bulky TM that varies from hard & gritty to rubbery; tan-white to fish flesh-like in appearance; grows with pushing margins into soft tissues; underlying cortex frequently thickened & irregular; TM may transgress cortex & extend into medullary cavity

### Sections to Be Submitted

- TM should be well sampled: 1 section per centimeter of greatest diameter; underlying cortex & medullary cavity

### Size

- Range: 3-18 cm (average: 9.8 cm)

## MICROSCOPIC

### Histologic Features

- Neoplastic bone-forming component usually predominates; TM cells show severe cytologic atypia & atypical mitoses; neoplastic cells intimately associated with coarse lace-like or poorly formed trabeculae of woven bone; necrosis may be present
- High-grade malignant cartilaginous & fibroblastic components may be present; linear trabeculae of benign reactive woven bone course through TM
- Cortex may be thickened by reactive bone or thinned by osteoclasts stimulated by presence of TM; may invade haversian systems & infiltrate medullary cavity

## DIFFERENTIAL DIAGNOSIS

### Osteoma

- Can rarely arise on surfaces of long tubular bones; neoplastic bone is cortical & lamellar in appearance; hypocellular & no cytologic atypia

### Parosteal Osteosarcoma

- TM cells do not demonstrate severe cytologic atypia unless area of dedifferentiation is present; usually arises on posterior surface of distal femur; contains significantly more ossification than high-grade surface osteosarcoma

### Periosteal Osteosarcoma

- Composed of predominately chondrosarcomatous component (chondroblastic osteosarcoma); arises underneath periosteum

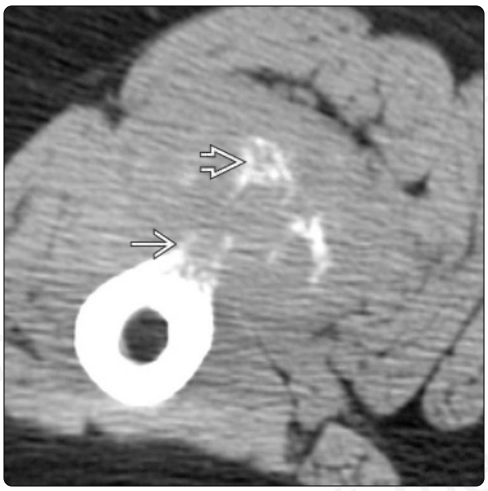
## SELECTED REFERENCES

1. Staals EL et al: High-grade surface osteosarcoma: a review of 25 cases from the Rizzoli Institute. Cancer. 112(7):1592-9, 2008

### Eroding Cortex

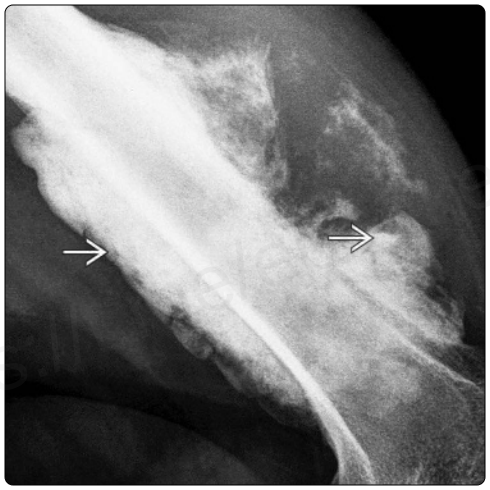


### Surface Osteosarcoma of Femur



**(Left)** *Plain radiograph of high-grade surface osteosarcoma shows a tumor on the surface of the bone. Intratumoral mineralization is present ➔. The tumor erodes the cortex.* **(Right)** *Axial CT of a high-grade surface osteosarcoma demonstrates an ovoid mass present on the surface of the femur. Mineralization is present at the base of the tumor ➔ as well as in the central portion of the neoplasm ➔.*

### Heavily Mineralized Surface Osteosarcoma

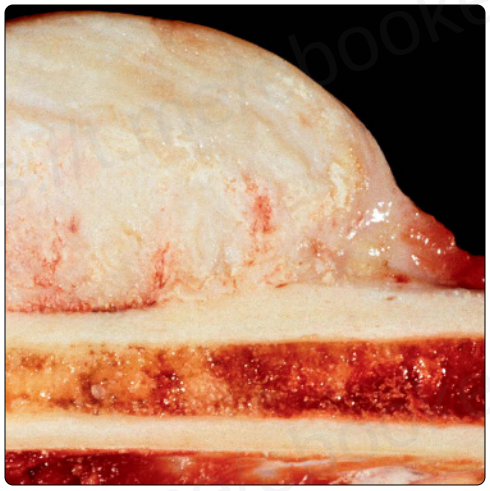


### Surface Osteosarcoma of Femur

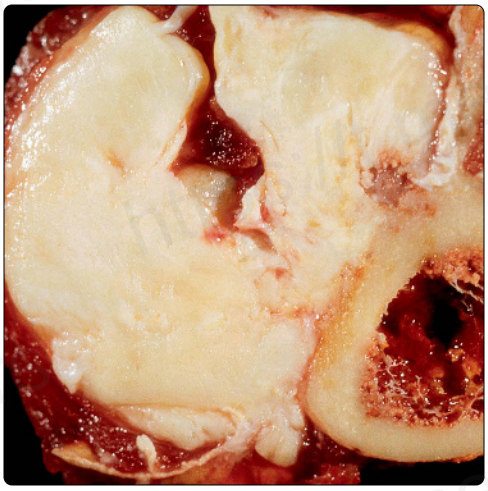


**(Left)** *Plain radiograph of a high-grade osteosarcoma of the femur shows that the tumor is heavily mineralized ➔. The tumor adjacent to the cortex shows significantly more mineralization than the superficial aspect of the neoplasm.* **(Right)** *An eccentric high-grade surface osteosarcoma is seen involving the diaphyseal surface of the femur. The tumor is tan-yellow and well circumscribed. Although the tumor closely adheres to the cortex, it does not infiltrate underlying medullary cavity.*

### Broad-Based Surface Osteosarcoma

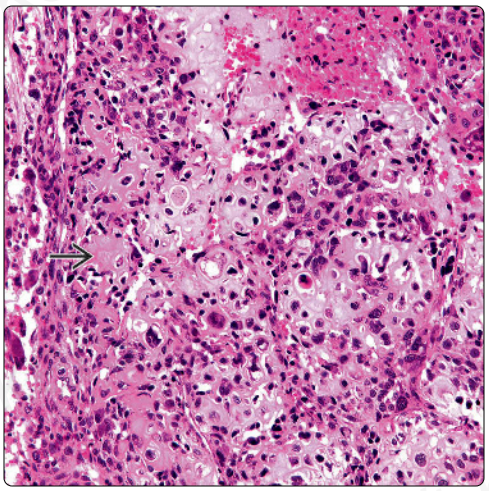


### Fleshy Surface Osteosarcoma

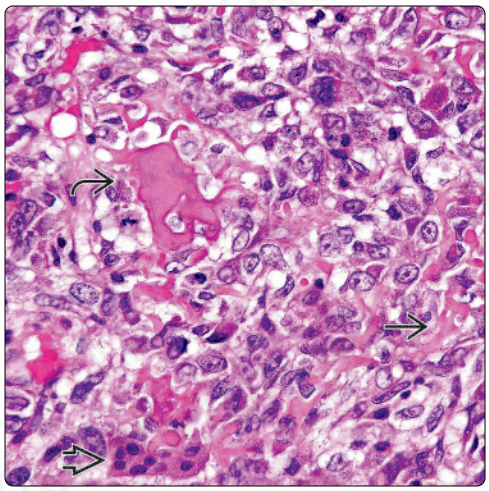


**(Left)** *Gross photograph of a high-grade surface osteosarcoma reveals a homogeneous cut surface of the tumor. There is a broad-based attachment to the femur. The tumor does not infiltrate the underlying cortex.* **(Right)** *Gross photograph of a high-grade surface osteosarcoma shows a gray-white homogeneous cut surface of a tumor. The tumor involves roughly 1/2 of the circumference of the femur. The cortex and medullary cavity are free of tumor.*

Marked Pleomorphism

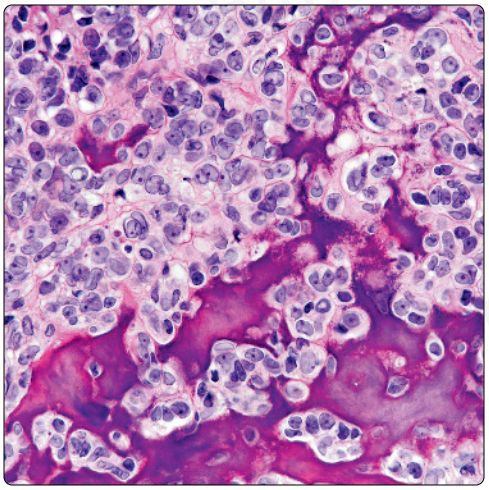


Epithelioid Appearance of Tumor Cells

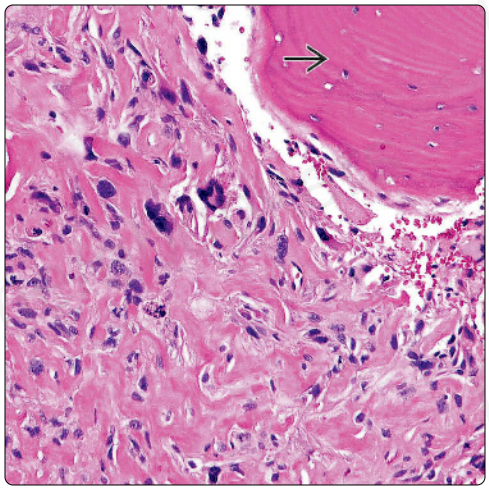


**(Left)** *Photomicrograph shows a high-grade osteosarcoma. The tumor cells show marked pleomorphism and are hyperchromatic. The tumor cells line the extracellular eosinophilic osteoid material. (Right) The neoplastic cells of this high-grade osteosarcoma have an epithelioid appearance. Intratumoral osteoid is present. Focally, the osteoid is deposited in a lace-like network. Occasional osteoclast-type giant cells are also present.*

Abundant Bone Formation

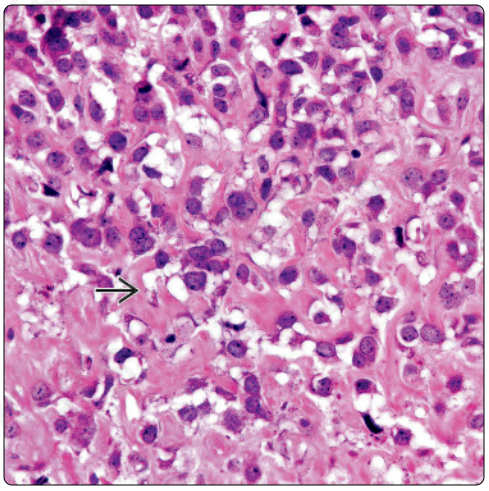


Marked Pleomorphism

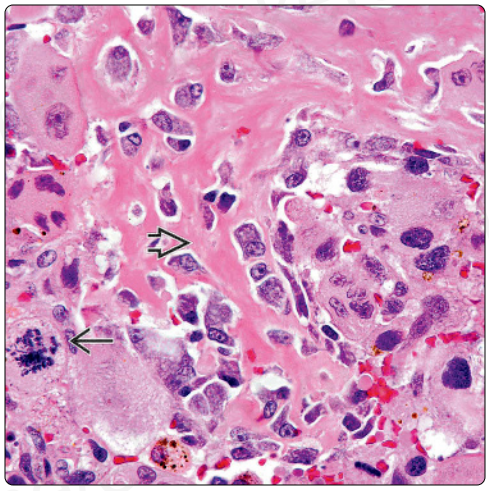


**(Left)** *Photomicrograph of a high-grade osteosarcoma, small cell variant, shows small to medium-sized tumor cells with hyperchromatic nuclei and scant cytoplasm. Abundant intratumoral bone formation by the tumor cells is identified.* **(Right)** *This high-grade osteosarcoma shows marked nuclear atypia and a densely collagenous background. Note the focus of preexisting lamellar bone. High-grade osteosarcomas, such as this, are generally incapable of producing lamellar bone.*

High-Grade Surface Osteosarcoma



Marked Anaplasia and Atypical Mitosis



**(Left)** *This high-grade osteosarcoma presented exclusively on the surface of the bone and did not infiltrate the cortex. The extracellular eosinophilic stroma likely represents tumor bone.* **(Right)** *The neoplastic cells of this high-grade osteosarcoma demonstrate an epithelioid appearance and marked anaplasia. Some of the tumor cells are entrapped within osteoid. An atypical mitotic figure is present.*

# Secondary Osteosarcoma

KEY FACTS

## TERMINOLOGY

- Osteosarcoma arising in association with benign tumor or diseased bone

## ETIOLOGY/PATHOGENESIS

- Paget disease
- Post radiation
- Other benign osseous lesions: Fibrous dysplasia, bone infarct, metallic prosthetic implant reaction

## CLINICAL ISSUES

- Elderly patients, typically > 50 years of age
- Prognosis is poor
- Progressively enlarging painful mass
- Pathologic fracture

## IMAGING

- Permeative and destructive lesion
- Poorly defined without sclerotic rim

## MACROSCOPIC

- Paget osteosarcoma
  - Distribution of disease is similar to that of Paget disease
  - Osteosarcoma accounts for > 80% of Paget sarcoma
- In osteosarcoma arising in infarcted bone, high-grade tumor can be seen adjacent to yellow infarcted areas of bone
- In osteosarcoma arising in association with prosthesis, tumor is seen surrounding prosthetic material
- ~ 1/2 of cases of fibrous dysplasia with osteosarcoma have received radiation

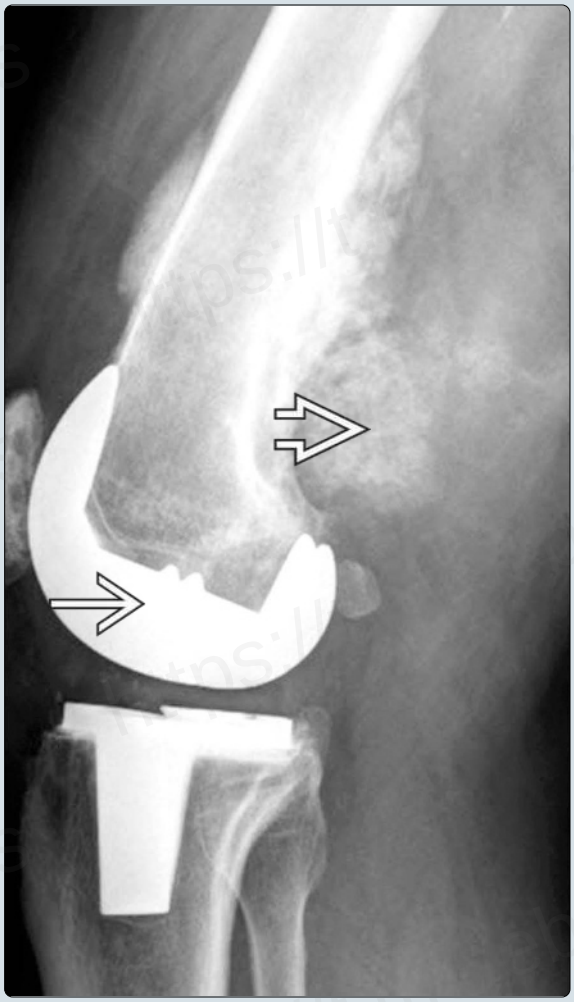
## MICROSCOPIC

- Histologic features are similar to high-grade intramedullary osteosarcoma

## TOP DIFFERENTIAL DIAGNOSES

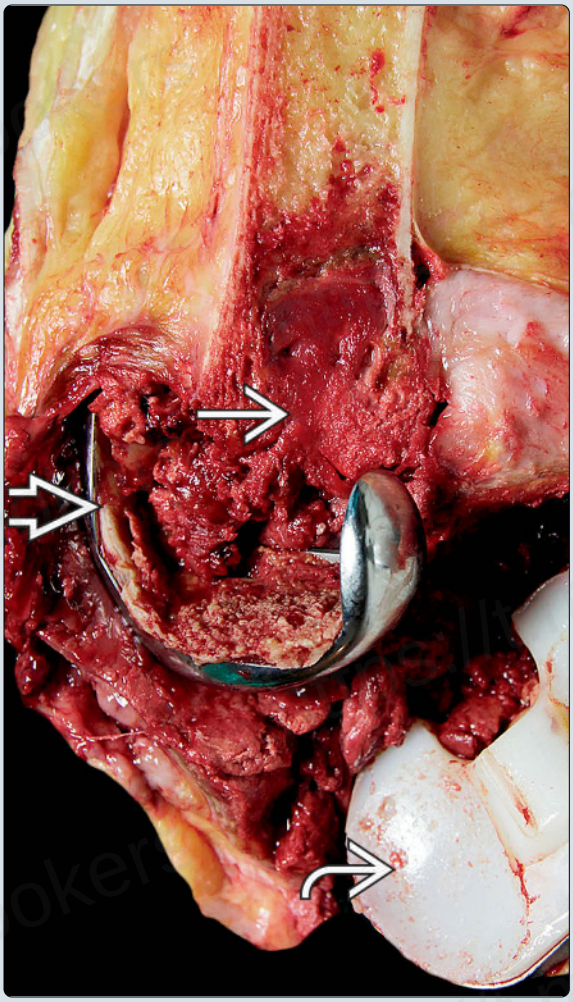
- Fibrosarcoma

**Osteosarcoma Adjacent to Knee Prosthesis**



*Large osteosarcoma that arose in the distal femur adjacent to a prosthetic knee joint is shown. The tumor is poorly defined with areas of mineralization that are most prominent in the soft tissues. The tumor involves the epiphysis adjacent to the prosthesis.*

**Osteosarcoma Next to Knee Prosthesis**



*A resected distal femur containing an osteosarcoma of the distal femur that extends to the femoral component of the prosthetic knee is shown. The hemorrhagic tumor has destroyed the bone. The tibial component is also seen.*

## TERMINOLOGY

### Definitions

- Osteosarcoma arising in association with benign tumor or diseased bone

## ETIOLOGY/PATHOGENESIS

### Paget Disease

- Incidence of sarcomatous degeneration: 0.70-0.95%
- Osteosarcoma accounts for > 80% of Paget sarcoma
- Tumor usually develops in patients with severe disease

### Post Radiation

- Most common radiation-induced sarcoma is osteosarcoma, followed by undifferentiated pleomorphic sarcoma
- Constitutes 3.4-5.5% of all osteosarcomas

### Other Benign Bone Lesions

- Very uncommon
  - Bone infarcts, reaction to metallic prosthetic implant, fibrous dysplasia, enchondroma
    - Biomaterial used in prosthesis have been shown to be potentially carcinogenic in animal studies
    - Most common implant-related sarcoma is pleomorphic fibrosarcoma followed by osteosarcoma
    - ~ 1/2 of cases of fibrous dysplasia with osteosarcoma have received radiation

## CLINICAL ISSUES

### Epidemiology

- Age
  - Elderly, typically > 50 years
  - Occasionally, young individuals with malignancy treated with radiation
  - Paget osteosarcoma: Mean age: 66 years

### Presentation

- Progressively enlarging painful mass
- Pathologic fracture
- Postradiation osteosarcoma
  - Latent period from radiation is long; median: 11 years
    - Rarely as little as 2 years
    - Latency inversely related to radiation dose

### Prognosis

- Poor
  - In one series, 5-year survival of Paget osteosarcoma was 8%
    - Unlike conventional osteosarcoma, outcome for these patients has remained unchanged over last several decades
- In recent study, overall survival for radiation-induced sarcoma was 85% at 1 year, 51% at 2 years, 48% at 3 years, and 45% at 5 years
  - Overall survival for postradiation bone sarcomas is higher compared to postradiation soft tissue sarcomas

## IMAGING

### Radiographic Findings

- Permeative and destructive lesion with periosteal reaction
- Poorly defined without sclerotic rim
- Mixed lytic and blastic mass that transgresses cortex and forms large soft tissue tumors
  - Paget osteosarcoma is more frequently lytic
- Radiation osteitis seen in postradiation osteosarcoma

## MACROSCOPIC

### General Features

- Pelvic and axial skeletons are more commonly affected than long bones
- Paget osteosarcoma
  - Distribution of disease is similar to that of Paget disease
  - Long bones affected in 2/3 of cases, flat bones in 1/3 of cases
  - 15% of Paget sarcoma involves skull
  - Occasionally, osteosarcoma is multifocal

## MICROSCOPIC

### Histologic Features

- Histologic features are similar to high-grade intramedullary osteosarcoma
- Paget osteosarcoma
  - Often osteoblastic or fibroblastic
    - In one series, 61% were osteoblastic, 31% fibroblastic, and 8% chondroblastic
  - Osteoclast-type giant cells may be prominent
  - Adjacent bone shows evidence of Paget disease
    - Mosaic pattern of lamellar bone
    - Osteoclastic activity and numerous resorption pits
    - Osteoclasts are large with numerous nuclei
    - Burnt-out disease is osteosclerotic
  - Tumors are always high grade
- Postradiation osteosarcoma
  - Radiation osteitis may be seen
- In osteosarcoma arising in bone infarct, tumor is seen adjacent to infarcted bone and bone marrow

## DIFFERENTIAL DIAGNOSIS

### Fibrosarcoma

- Lacks osteoid directly abutted by tumor cells

### Fracture Callus

- Osteoid is rimmed by nonneoplastic osteoblasts
- Fracture site shows fibrocartilage, a finding not seen in either osteosarcoma or chondrosarcoma

### Chondrosarcoma

- Lacks osteoid rimmed by neoplastic cells

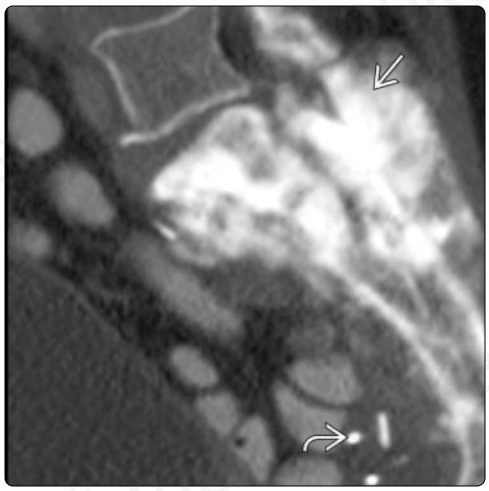
### Pagetoid Bone in Other Disease

- Pagetoid appearance is seen in osteosarcoma, including intramedullary osteosarcoma not associated with Paget disease

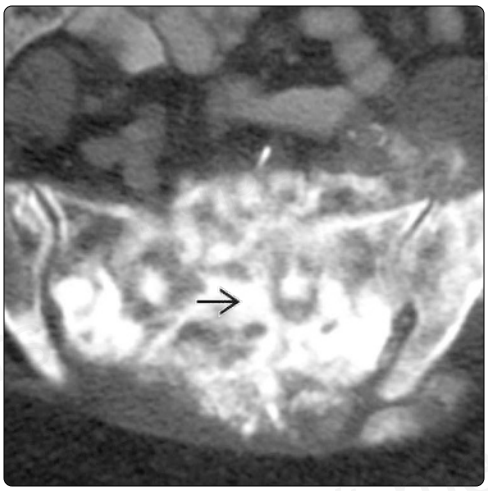
## SELECTED REFERENCES

1. Mankin HJ et al: Paget's sarcoma: a historical and outcome review. Clin Orthop Relat Res. 438:97-102, 2005

### Osteosarcoma in Radiated Bone

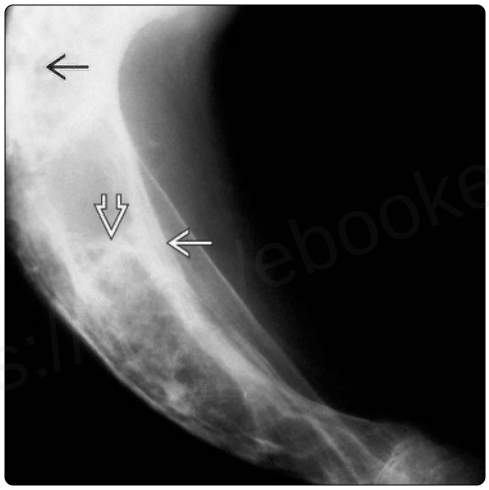


### Osteosarcoma Arising in Irradiated Bone

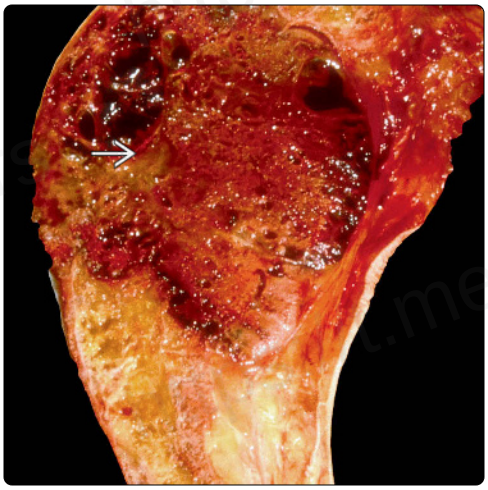


**(Left)** *Sagittal reformatted CT scan demonstrates a high-grade osteosarcoma arising in the sacrum previously irradiated for colonic adenocarcinoma. The mineralized tumor ➔ destroys the vertebral body and extends into the posterior elements. Note the surgical clips from the previous colonic resection ➔.* **(Right)** *Axial CT shows a large radiodense osteosarcoma ⇨ arising in irradiated bone for a previously diagnosed colonic adenocarcinoma.*

### Osteosarcoma in Paget Disease

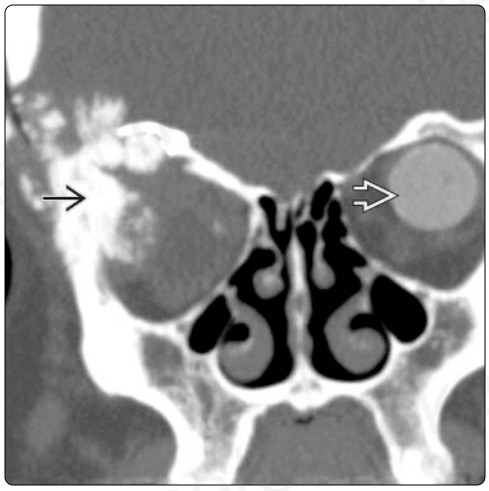


### Hemorrhagic Tumor in Paget Disease

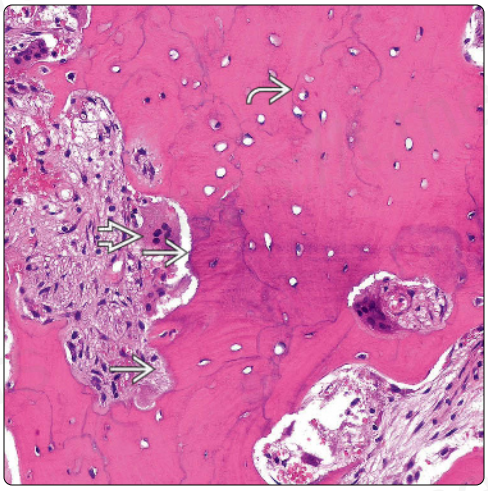


**(Left)** *Lateral radiograph of an advanced case of Paget disease shows diffuse involvement of the tibia. Note the enlarged, coarsened cortex ➔ and trabeculae ➔ and anterior bowing of the bone. The lytic and blastic destructive lesion in the proximal tibia ⇨ represents an osteosarcoma.* **(Right)** *Gross image shows a conventional osteosarcoma arising in Paget disease of bone. The tibia is expanded, and the cortex is not clearly visualized. The large hemorrhagic mass represents an osteosarcoma ➔.*

### Retinoblastoma-Associated Osteosarcoma

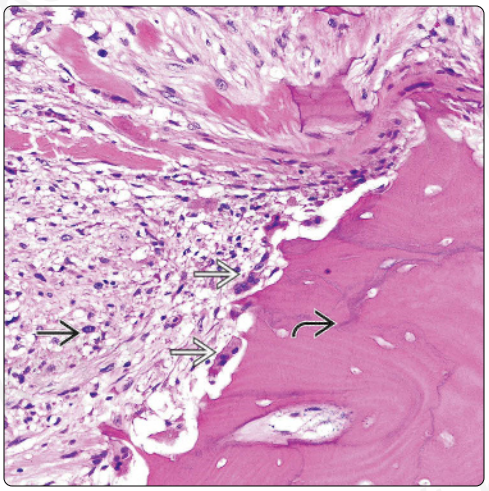


### Cement Lines in Paget Disease of Bone

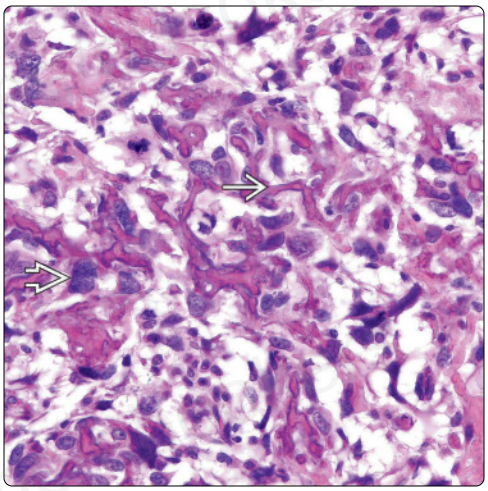


**(Left)** *This patient had a previously diagnosed bilateral retinoblastoma that was treated with exenteration and radiation. The large mineralized tumor ⇨, representing the subsequent osteosarcoma, extends into the orbit and cranial cavity and permeates the underlying bone. Note the orbital prosthesis ➔.* **(Right)** *The diagnostic feature of Paget disease is the mosaic pattern of units of lamellar bone delineated by cement lines ➔. Note the large osteoclasts ➔ and scalloped bone surfaces ➔.*

### Osteosarcoma in Paget Disease

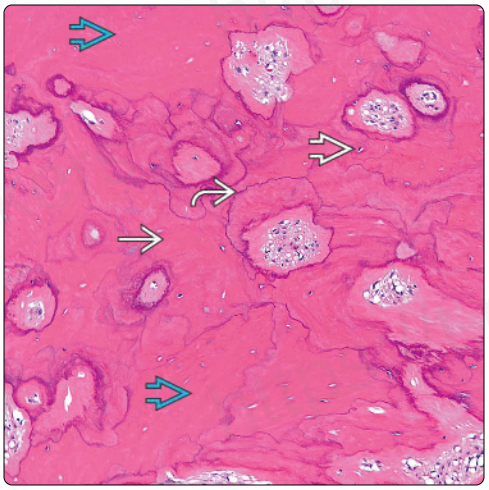


### High-Grade Osteosarcoma

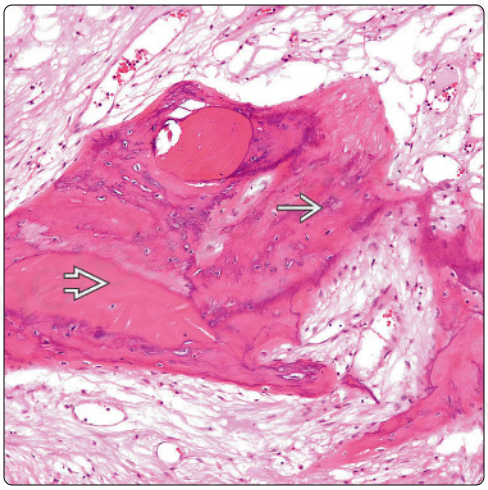


**(Left)** *A high-grade osteosarcoma arising in a pagetic bone is seen. The adjacent preexisting lamellar bone shows a mosaic pattern formed by cement lines. A leading edge of osteoclasts is seen adjacent to the bone. Unequivocal osteoid abutted by neoplastic cells is not appreciated in this H&E.* **(Right)** *High-grade osteosarcoma arising in an individual with Paget disease is shown. A lace-like pattern of osteoid is seen. The osteoid is directly abutted by tumor cells showing marked nuclear atypia.*

### Osteosarcoma With Reversal Lines

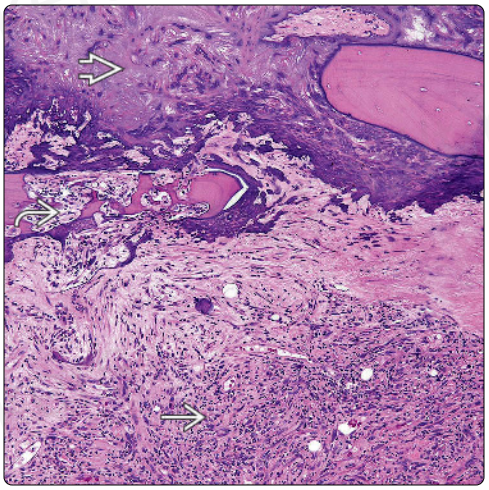


### Radiation Osteitis

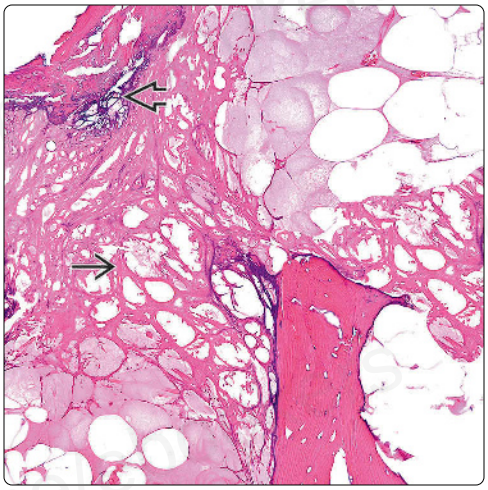


**(Left)** *A high-grade sclerotic osteosarcoma with abundant bone deposition is shown. The neoplastic cells show no atypia, the so-called normalization. Prominent reversal lines are seen in the neoplastic component. Note the preexisting lamellar bone is encased by tumor.* **(Right)** *Radiation osteitis is manifest by marrow fibrosis and reactive woven bone surrounded by preexisting lamellae. Fat necrosis, marrow fibrosis, and bone remodeling may also be present.*

### Osteosarcoma Arising in Bone Infarct



### Bone Infarct



**(Left)** *An osteosarcoma arising in the tibia that was affected by a previous bone infarction is seen. The necrotic tissue has undergone extensive dystrophic calcification. The preexisting trabeculae have been eroded by previous osteoclastic activity.* **(Right)** *A bone infarction is composed of necrotic fat and bone. Some of the dead adipocytes have their cell boundaries delineated by eosinophilic material that can sometimes appear as a cuticle. Dystrophic calcification is present.*

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SECTION 3

# Benign Cartilage Tumors




| | |
|---|---|
| Vascular Cartilaginous Hamartoma of Chest Wall | **82** |
| Osteochondroma | **84** |
| Multiple Hereditary Osteochondromatosis | **94** |
| Enchondroma | **98** |
| Enchondromatosis | **110** |
| Periosteal Chondroma | **116** |
| Chondroblastoma | **120** |
| Chondromyxoid Fibroma | **128** |


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# Vascular Cartilaginous Hamartoma of Chest Wall

KEY FACTS

## TERMINOLOGY

- Vascular cartilaginous hamartoma

## CLINICAL ISSUES

- Typically arises from 1 or multiple ribs in fetus or early infancy
- 75% of affected children are < 1 year of age
- Chest wall deformities
- Often require complete surgical resection
- Prognosis is excellent

## IMAGING

- Large expansile cystic mass
- Fluid-fluid levels may be present
- Contains areas of mineralization
- Low and high T1- and T2-weighted signal intensity reflecting solid and cystic components

## MACROSCOPIC

- Well-circumscribed, tan-red cartilaginous mass
- Numerous blood-filled cystic spaces

## MICROSCOPIC

- Composed of collage of tissues: Nodules of hyaline cartilage surrounded by proliferating fibrovascular tissue and variably sized cysts
- Islands of hyaline cartilage resemble disorganized growth plate
- Blood-filled cystic spaces may dominate lesion
- Spindle cell component may be hypercellular and admixed with woven bone

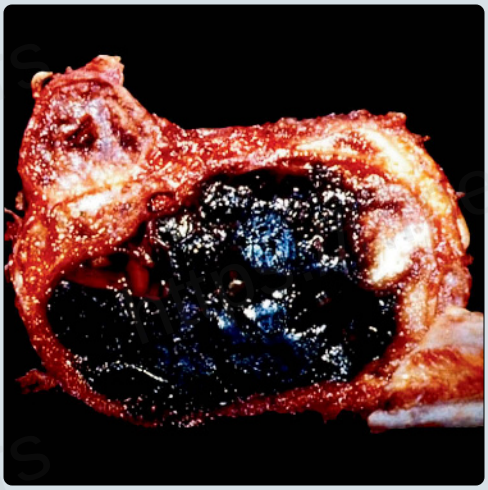
## DIAGNOSTIC CHECKLIST

- Admixture of growth plate-like cartilage, cysts, spindle cells, and woven bone

**Hamartoma of Rib**

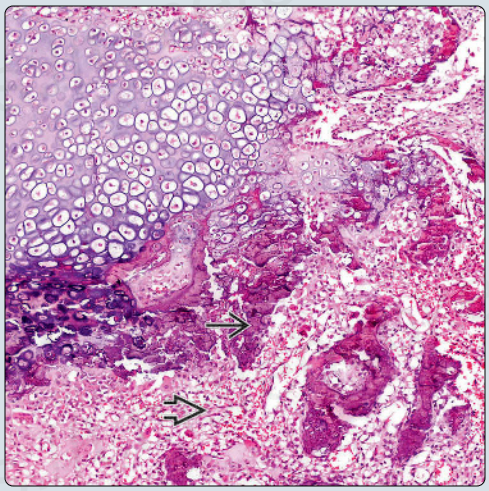


**Blood-Filled Cysts**

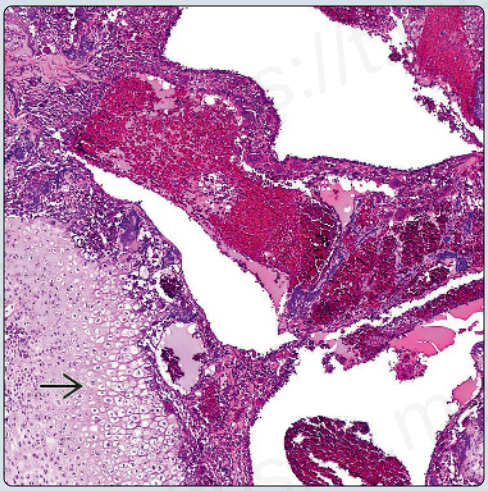


**(Left)** *Radiograph of a vascular cartilaginous hamartoma expanding a rib shows a tumor that is lytic, well circumscribed, surrounded by a layer of reactive bone, and containing internal linear trabeculations.* **(Right)** *Resected rib contains a vascular cartilaginous hamartoma, which appears as a well-circumscribed bloody mass. Portions of the tumor are solid, consisting of red-tan tissue. (Courtesy I. Amstalden, MD.)*

**Growth Plate-Like Cartilage and Bone**



**Blood-Filled Cysts**



**(Left)** *Hyaline cartilage of the tumor undergoes enchondral ossification, and the woven bone trabeculae are surrounded by plump osteoblasts. The spindle cell area is hypercellular and are cytologically banal.* **(Right)** *The tumor contains large cystic spaces that are often filled with blood resembling an aneurysmal bone cyst. The walls of the cysts harbor nodules of growth plate-like cartilage and fascicles of spindle cells.*

## TERMINOLOGY

### Synonyms

- Chest wall hamartoma
- Vascular hamartoma of infancy
- Chondromatous hamartoma of chest wall

### Definitions

- Hamartomatous tumor of rib that usually develops during fetal life or early infancy

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Rare
  - ~ 80 cases have been described in literature
- Age
  - Fetal life or early infancy
  - 75% of affected children are < 1 year of age
  - Rarely reported in adults
- Sex
  - Males slightly more affected than females

### Site

- Typically arises in 1 or multiple ribs
  - Rarely originates in other sites, including vertebral column
- Some lesions described as nasal chondromesenchymal hamartoma and osteochondromyxoma of bone may also be variants of this lesion

### Presentation

- Asymptomatic
- Chest wall deformities
- Respiratory distress

### Natural History

- Growth that plateaus; spontaneous regression documented

### Treatment

- Often require complete surgical resection

### Prognosis

- Prognosis is excellent
- Recurrence results from incomplete resection
- Rare fatalities from respiratory complications

## IMAGING

### Radiographic Findings

- Large expansile cystic mass
  - Fluid-fluid levels may be present
- Contains areas of mineralization
- Some cases may extend into adjacent soft tissues
  - Raises concern for more aggressive lesion

### MR Findings

- Low and high T1- and T2-weighted signal intensity reflecting solid and cystic components

### CT Findings

- Expansile mass with areas of mineralization and bone destruction

## MACROSCOPIC

### General Features

- Well-circumscribed mass
- Tan-white-red solid areas
- Glistening hyaline cartilage may be visible
- Focally gritty
- Numerous blood-filled cystic spaces
  - May dominate lesion

## MICROSCOPIC

### Histologic Features

- Collage of tissues that include
  - Nodules of hyaline cartilage surrounded by proliferating fibrovascular tissue
  - May contain woven bone and variably sized cysts
- Islands of hyaline cartilage
  - Frequently resemble disorganized growth plate
  - Can undergo endochondral ossification
  - Cellular with only mild cytological atypia
- Cystic spaces resemble aneurysmal bone cyst and may predominate
  - Lumina of cysts are lined by fibroblasts and collagen; lack endothelial cell lining
- Spindle cell component may be hypercellular and mitotically active
  - Cytologically bland and normal mitoses
  - Highly collagenous areas may be present
- Blood vessels may be numerous
  - Usually consist of small-caliber capillaries with scattered larger dilated vascular channels
- Variable amount of reactive bone often present

## ANCILLARY TESTS

### Immunohistochemistry

- Chondrocytes are positive for S100
- Spindle cells are positive for smooth muscle actin

## DIFFERENTIAL DIAGNOSIS

### Aneurysmal Bone Cyst

- Lack cartilaginous nodules

### Chondrosarcoma and Osteosarcoma

- Contains cytologically malignant matrix forming cells

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Admixture of growth plate-like cartilage, cysts, spindle cells, and woven bone

## SELECTED REFERENCES

1. Amstalden EM et al: Chondromatous hamartoma of the chest wall: description of 3 new cases and literature review. Int J Surg Pathol. 14(2):119-26, 2006

# Osteochondroma

KEY FACTS

## TERMINOLOGY

- Benign surface cartilage-capped tumor arising in metaphysis
- Accounts for 36-50% of benign tumors surgically treated

## ETIOLOGY/PATHOGENESIS

- Neoplastic process; mutations in *EXT1* and *EXT2* genes
- Majority occur sporadically

## CLINICAL ISSUES

- Most patients in 2nd decade of life at time of diagnosis
- Typically arise in metaphysis of bones derived from endochondral ossification
- Treated by observation or simple excision
- May be painful
- Osteochondroma (OCE) exhibits majority of growth while physeal plates are open
- Malignant degeneration of solitary OCE is very uncommon (0.4-2.0%)

## IMAGING

- Surface lesion with continuity of cortices and medullary cavity of bone and lesion

## MACROSCOPIC

- Cartilage cap of variable thickness; ranges from < 1 to > 2 inches in depth
- Overall size ranges from 3-6 cm

## MICROSCOPIC

- Outer fibrous layer is perichondrium
- Cartilage cap mimics growth plate and undergoes ossification

## TOP DIFFERENTIAL DIAGNOSES

- Bizarre parosteal osteochondromatous proliferation
- Periosteal myositis ossificans
- Surface (periosteal) chondroma
- Surface osteosarcoma (parosteal osteosarcoma)

**Sessile Tumor**



*A plain radiograph shows a sessile osteochondroma (OCE) of the distal anterior femur. There is no stalk, but the diagnostic features of cortical and medullary continuity are present, although more difficult to recognize.*

**Blue-White Cartilage Cap**



*A gross image shows an OCE. The sessile lesion has a hyaline cartilage cap composed of blue, glistening cartilage. The cartilage undergoes enchondral ossification forming cancellous bone.*

## TERMINOLOGY

### Abbreviations

- Osteochondroma (OCE)

### Synonyms

- Exostosis
- Osteocartilaginous exostosis

### Definitions

- Benign, cartilage-capped tumor that originates in metaphysis or region of apophysis
- Arises on surface of bones and enlarges through process of endochondral ossification
- OCE occurs in 2 clinical settings
  - As solitary lesion
  - Multiple lesions (multiple hereditary osteochondromatosis)

## ETIOLOGY/PATHOGENESIS

### Neoplastic Process

- May occur sporadically, but when manifestation of hereditary multiple OCEs (autosomal dominant genetic disorder), they tend to be polyostotic and bilaterally symmetrical
- OCEs were believed to develop from lateral displacement or redirection of growth plate or defects in surrounding periosteal cuff of bone
  - Based on observation that OCEs never arise on surface of existing cortex and were induced experimentally in animals by manipulating the growth plate
- Chondrocytes in cap have inactivating mutations of *EXT1* and *EXT2* genes on chromosomes 8q24 and 11p11-12
  - Chondrocytes represent monoclonal cellular proliferation and indicates that neoplastic component of OCE resides in cartilage cap
  - Mutation disrupts production of heparan sulfate, which is important in growth plate and ossification
- Involvement of *EXT3* on chromosome 19p seen in some cases
- Genetic abnormalities of OCE have not been identified in dysplasia epiphysealis hemimelica or metachondromatosis
- Small minority of OCE associated with previous radiation
  - Most patients are young
    - 25% of patients ≤ 5 years who receive total-body radiation develop OCE
- Patients with metachondromatosis have both OCE and enchondromas

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Most common primary bone tumor
  - Accounts for 36-50% of benign bone tumors and 8.5-15.0% of all primary neoplasms of bone
  - ~ 80-85% are solitary
- Age
  - Most patients are in their 2nd decade of life at time of diagnosis
    - Incidence: 35/1 million individuals 0-18 years
    - Age range: 8-77 years, average: 21 years
- Sex
  - Male preponderance; M:F = 1.5-2:1

### Site

- Typically arise in appendicular skeleton
  - In metaphysis of bones derived from endochondral ossification
    - Distal femur, proximal tibia, proximal humerus
- Rarely arise in epiphysis
  - Known as Trevor disease or dysplasia epiphysealis hemimelica in this location
- Can involve flat bones, such as ilium and scapula
- Rare on small bones of hands and feet and vertebrae; do not arise on craniofacial skeleton

### Presentation

- Many are asymptomatic
  - Incidental finding on imaging studies
- Slowly enlarging firm mass present for many years
- May be painful
  - Impingement upon adjacent neurovascular structures
  - Inflamed overlying bursa: Inflammatory bursitis
  - Fracture of stalk
- Interferes with range of motion

### Natural History

- Slow growth that usually ceases at puberty
  - OCE exhibit majority of growth while physeal plates are open
- Malignant transformation should be considered if OCE grows rapidly

### Treatment

- Small and asymptomatic OCE do not require intervention
  - May have complications that cause symptoms requiring removal
- Excision usually adequate therapy
  - Cortex is transected near base of lesion
  - Overlying bursa should be removed with cartilage cap
  - If any perichondrium or cartilage cap is left behind, then lesion may recur

### Prognosis

- Malignant degeneration of solitary OCE is very uncommon (0.4-2.0%)
- Dedifferentiation is exceedingly rare

## IMAGING

### Radiographic Findings

- Arises from surface of bone
- Cortices of lesion and underlying bone and their marrow cavities in direct continuity
- Lesion points away from nearest joint in reaction to forces exerted by muscles and tendons
- Cartilaginous surface is lobulated and may contain calcifications
- Base can be narrow or broad (sessile lesion)

### MR Findings

- T1-weighted image shows similar signal intensity of medullary cavity of lesion and underlying bone



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- T2-weighted image shows high signal intensity cartilaginous cap
  - Low signal intensity surrounding cap represents perichondrium
- Helpful in evaluating thickness of cartilaginous cap

### CT Findings

- Nicely shows continuity of cortices and medullary cavity of OCE and underlying bone
- Useful in demonstrating thickness of cartilaginous cap
- Helpful in showing bursa formation

### Bone Scan

- Hot in growing individuals
- In adults, OCEs are often not hot on bone scan
  - Exceptions: Fracture, bursitis, malignant transformation

## MACROSCOPIC

### General Features

- Mushroom-shaped
- Outer layer consists of thin sheath of fibrous tissue that overlies pearly, gray-white cartilaginous cap
  - In older individuals, cartilaginous cap may be very attenuated or gone
  - May contain gritty areas of calcification or cystification
- Cartilage cap of variable thickness; ranges from < 1 inch to several inches in depth
  - Surface of cap is smooth and lobulated
  - Base has sharp but undulating margin with underlying cancellous bone
- Cartilage cap may demonstrate variable degrees of mineralization
  - In form of irregular stipples or ring-like calcifications
    - Due to partial or complete "framing" of cartilage lobules by ossification or amorphous mineralization
- Base of cartilage cap undergoes enchondral ossification and produces cancellous bone

### Size

- 1 cm to > 20 cm in greatest dimension
  - Average: 3-6 cm

## MICROSCOPIC

### Histologic Features

- Outer layer is perichondrium
  - Composed of dense fibrous tissue that overlies hyaline cartilage cap
  - Overall architecture recapitulates that of disorganized growth plate
- Peripheral cap least cellular with abundant hyaline matrix
- Cellularity of cartilage increases in deeper layers
- Chondrocytes arranged in vague columns and increase in size in deeper layers
- Chondrocytes exhibit minimal cytologic atypia
  - Scattered binucleate cells may be present
- Matrix calcifies at base of cap
- Chondrocytes undergo necrosis
  - Portions of mineralized cartilage are resorbed by osteoclasts at base of cap
  - Residual struts of cartilage matrix that are left behind act as scaffolding for bone deposition
- Newly formed trabeculae mimic primary spongiosa at base of normal growth plate
- Developing chondrosarcoma composed of thick hypercellular nodules of cartilage surrounded by fibrous septa
  - Chondrocytes exhibit varying degrees of atypia

## DIFFERENTIAL DIAGNOSIS

### Bizarre Parosteal Osteochondromatous Proliferation

- Contains reactive fibrous tissue overlying cellular cartilage cap that undergoes enchondral ossification
- Underlying cortex is intact

### Periosteal Myositis Ossificans

- Arises on surface of bone with intact underlying cortex
- Lacks well-formed cap of hyaline cartilage

### Surface (Periosteal) Chondroma

- Arises on intact cortex
- Composed of lobules of cartilage only without endochondral ossification

### Surface Osteosarcoma (Parosteal Osteosarcoma)

- Anchored to external surface of cortex without continuity between medullary cavity and center of mass
- Both can contain cartilaginous cap
  - Cartilaginous cap in parosteal osteosarcoma is more disorganized, although it can mimic OCE and may undergo endochondral ossification
- Parosteal osteosarcoma contains spindle-shaped malignant cells adjacent to neoplastic bone

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Typical radiographic findings with surface lesion sharing cortices and medullary cavity with underlying bone

### Pathologic Interpretation Pearls

- Has cartilaginous cap undergoing endochondral ossification
  - Identical to normal growth plate
- Some investigators believe that if cartilage cap is > 1 cm in thickness, then, by definition, it is malignant and has evolved into chondrosarcoma
  - We do not recommend that criteria
    - Cartilage cap should contain nodules of cartilage delineated by fibrous septa and show increased cellularity, cytologic atypia, &/or infiltration to be classified malignant

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3. Wiweger MI et al: Possible effects of EXT2 on mesenchymal differentiation--lessons from the zebrafish. Orphanet J Rare Dis. 9:35, 2014
4. Romeo S et al: Benign cartilaginous tumors of bone: from morphology to somatic and germ-line genetics. Adv Anat Pathol. 16(5):307-15, 2009

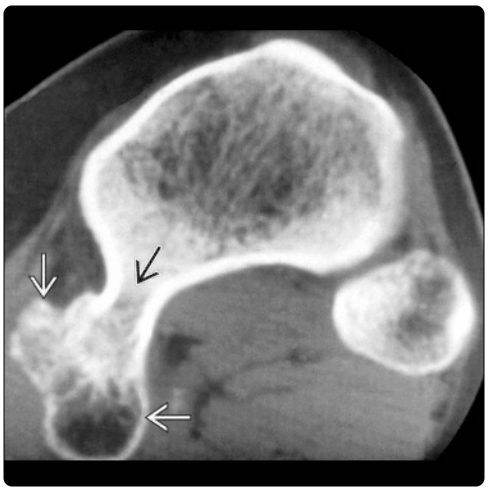



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**Pedunculated Mass**



**Continuity of Cortex and Medullary Cavity**



**(Left)** *A plain film of an OCE is shown arising from the proximal posterior tibia and pointing away from the joint. There is cortical continuity between the proximal tibial cortex and the stalk of the lesion.* **(Right)** *Axial CT of an OCE of the proximal tibia shows medullary continuity as well as cortical continuity between the OCE and underlying bone. Cancellous bone and marrow fat are present within the stalk of the OCE.*

**Protuberant Surface Mass**

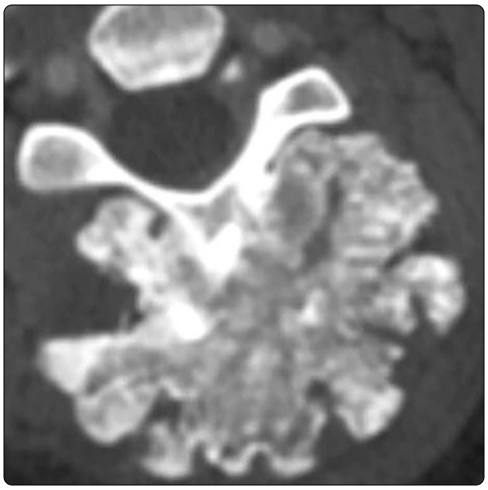


**Mass Extending Into Soft Tissue**



**(Left)** *OCE of the humerus is seen pointing perpendicular to the bone. The direction of the OCE is determined by muscle and tendon forces, and its direction is not a diagnostic feature. Note continuity of cortices and medullary cavity of the humerus and the lesion.* **(Right)** *Coronal reformation of an OCE demonstrates cortical and medullary continuity. Such lesions cause mechanical effects on adjacent soft tissues and bone, resulting in fracture, bursa formation, and bone remodeling.*

**Cauliflower-Like Mass**



**Mass of Posterior Elements of Spine**



**(Left)** *Axial CT demonstrates a large OCE that is originating from the posterior elements of the spine, an uncommon location. The tumor is well mineralized indicating abundant enchondral ossification has occurred.* **(Right)** *Accompanying sagittal T2-weighted MR of a large OCE that has a relatively thin cartilaginous cap is shown. The majority of the mass is composed of bone formed from enchondral ossification of the cartilage cap.*



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**Fracture of Base of Stalk**



**Mushroom-Shaped Tumor**



**(Left)** *An OCE is shown arising from the distal femur, which is capped by mineralized cartilage and grows in a direction away from the joint. There is a linear fracture through the base of the stalk* ➡. **(Right)** *OCE characteristically grows in a diagonal direction away from the nearby joint. This radiograph shows continuity between the stalk and underlying cortex of the femur* ⇨. *The opposite side of the femur has a small nonossifying fibroma* ➡.

**Broad-Based Mass**



**Large Overlying Bursa**



**(Left)** *Lateral radiograph demonstrates a broad-based OCE arising from the posterior metaphysis of the femur. The tumor has a trabecular pattern of mineralization* ➡, *which reflects enchondral ossification.* **(Right)** *Sagittal T2-weighted fat-saturated MR of an OCE with a large overlying bursa filled with fluid that manifests as increased intensity* ➡ *is shown. Note the continuity between the medullary cavity and cent of the tumor* ➡.

**Severe Distortion by Tumor**



**Bone Erosion**



**(Left)** *This patient has multiple hereditary osteochondromatosis and shows a large OCE of the 5th metatarsal that has produced a severe deformity of the involved toes.* **(Right)** *The OCE is originating from the 1st phalanx of the 2nd toe and impinges on the neighboring phalanx* ➡. *Overtime this has produced remodeling of the bone, which appears as a large excavation with a sclerotic margin.*



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**Sessile Tumor Eroding Fibula**

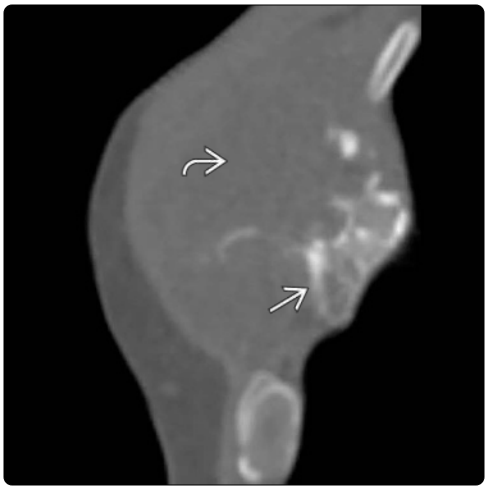


**Giant Osteochondroma**

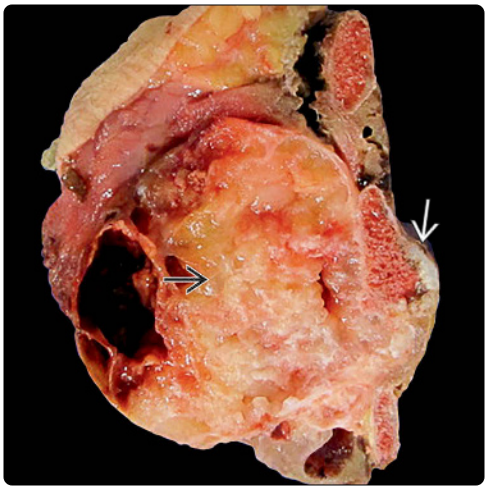


**(Left)** *A sessile OCE is seen arising from the distal tibia. The base of the lesion is broad and is in direct continuity with the underlying bone. The lesion is slow growing and has caused remodeling of the adjacent fibula.* **(Right)** *The patient is a 15 year-old boy with a giant OCE emanating from the diaphysis of the humerus. The tumor has areas of marked radiodensity, which reflects mineralized cartilage cap.*

**Dedifferentiated Osteochondroma of Rib**

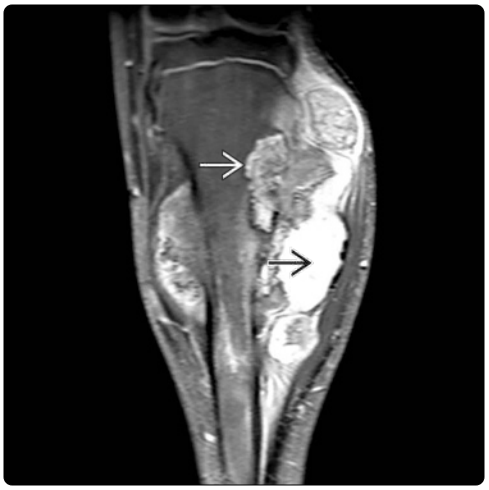


**Fleshy Mass**



**(Left)** *Reformatted sagittal CT shows a sessile OCE of a rib that has undergone dedifferentiation into a high-grade spindle cell sarcoma. The malignant component forms a large anterior chest wall mass.* **(Right)** *A large dedifferentiated chondrosarcoma (CSA) arises from an OCE of the rib, residual cartilage cap is present. The sarcoma is composed of lobules of hyaline cartilage and microscopic foci of a pleomorphic spindle cell sarcoma.*

**Malignant Transformation**



**Malignant Transformation**

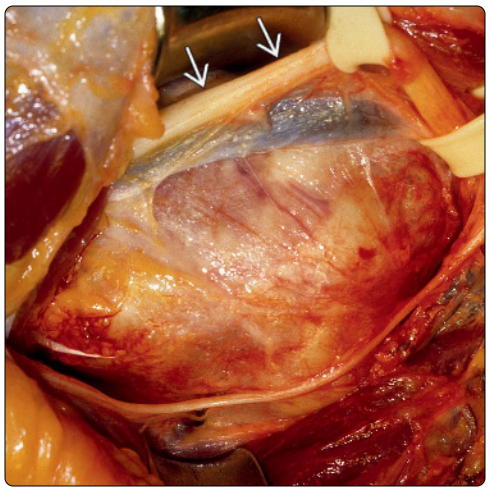


**(Left)** *This adolescent boy has a large OCE that has undergone malignant transformation into a low-grade conventional CSA. The coronal T2 fat-saturated sequence shows that the CSA is composed large masses of bright cartilage and is eroding into the tibia.* **(Right)** *In the 3D reformatted coronal CT, a large OCE is present that contains a thick unmineralized mass of cartilage that represents low-grade CSA and appears dark on the image. The mineralized element at the base is the underlying OCE.*

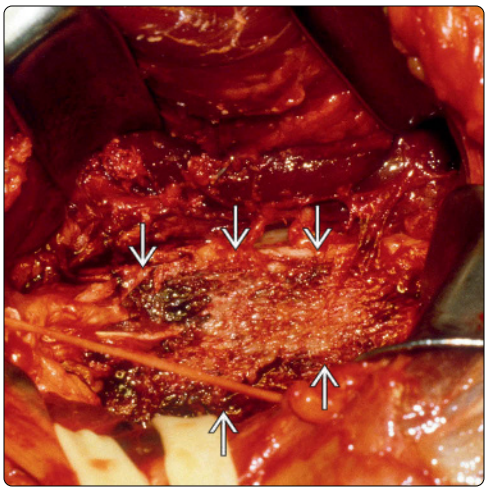


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**Cartilage Cap Exposed at Surgery**

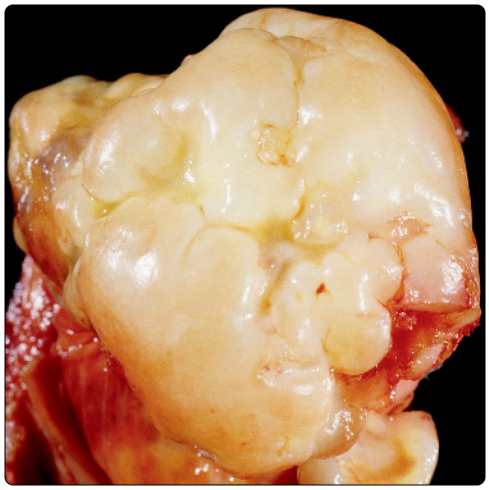


**Surgical Bed After Excision**

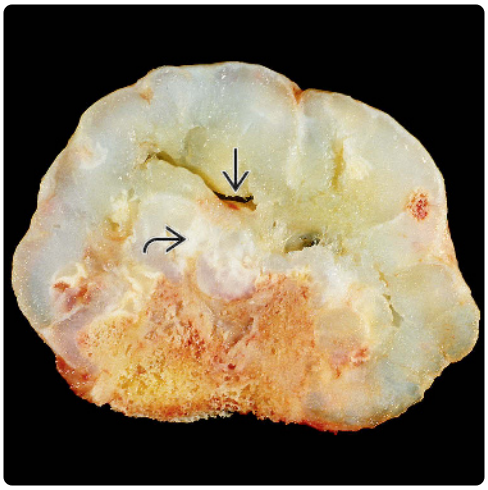


**(Left)** *Intraoperative view shows the cartilage cap of OCE covered by a translucent glistening perichondrium. The tumor is well delineated, and an adjacent nerve has been separated from the mass.* **(Right)** *Intraoperative image shows the resection bed of a previously excised OCE. The tumor has been shaved off from the underlying bone to which it was attached and from which it arose. The surgical bed consists of hemorrhagic cancellous bone.*

**Bosselated Surface**



**Thick Cartilage Cap**

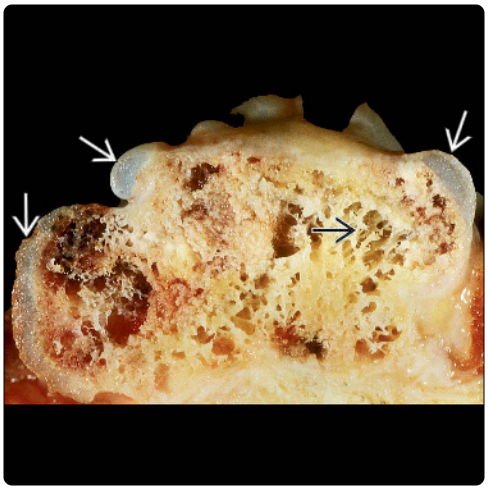


**(Left)** *Surface of a freshly excised OCE shows the mushroom-shaped cartilaginous surface. The cartilage is tan-white and glistening and has a well-demarcated nodular surface.* **(Right)** *OCE sectioned perpendicularly through the cartilaginous cap and underlying cancellous bone is shown. The hyaline cartilage cap is gray-blue and has undergone central degeneration. The basal portion of the cap is white and reflects mineralization of the cartilage.*

**Well-Formed Cartilage Cap**



**Osteochondroma Finishing Growth Phase**

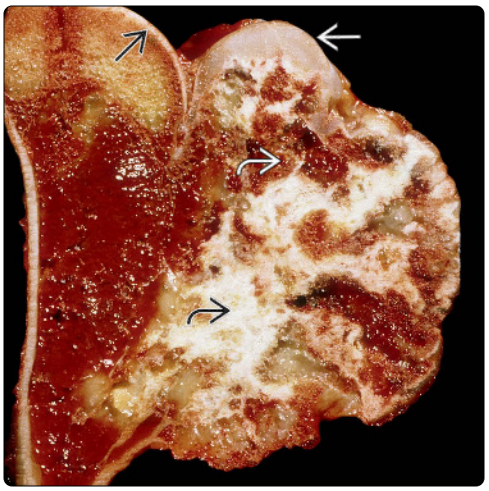


**(Left)** *A typical OCE that has a mushroom-shaped configuration and well-formed hyaline cartilage cap is seen. The cartilage cap overlies newly formed cancellous bone, which contains fatty marrow.* **(Right)** *OCE has large portions of the cartilage cap that have undergone complete enchondral ossification. Residual portions are still actively growing.*

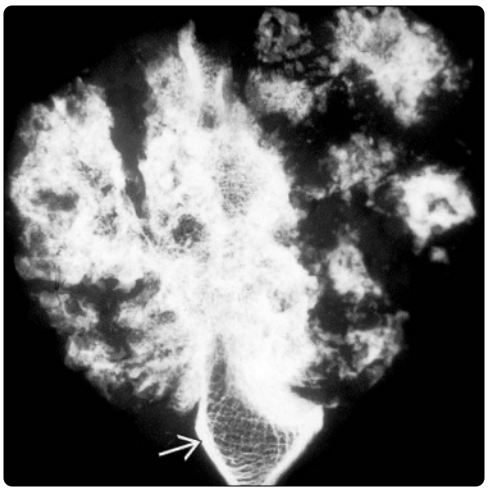


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### Large Mineralized Mass

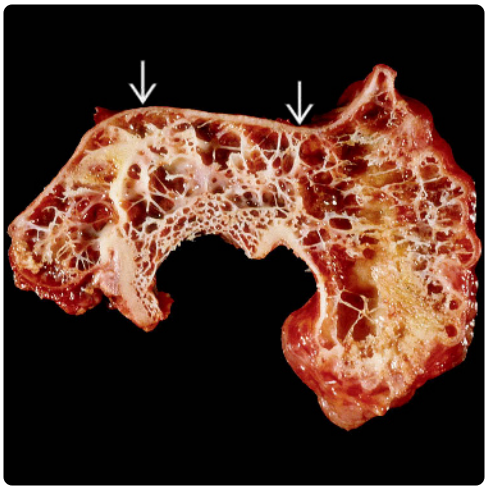


### Giant Mass With Mineralization

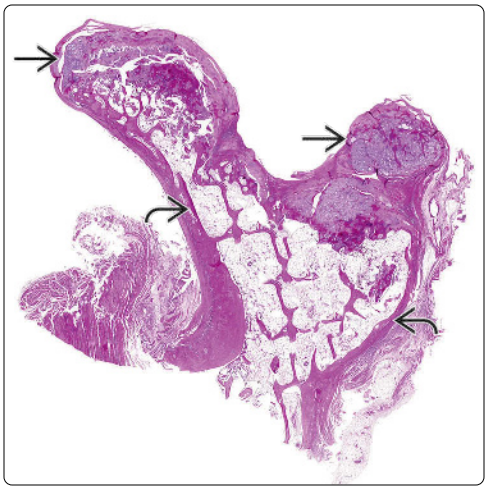


**(Left)** *A very large sessile OCE grows over a portion of articular surface. The hyaline cartilage cap has undergone calcification and enchondral ossification. Direct continuity between the marrow cavity and center of lesion is noted.* **(Right)** *Specimen radiograph shows a large OCE having a thick cartilaginous cap and attached stalk. The cartilage cap has undergone calcification and enchondral ossification, which are features of a benign lesion.*

### Complete Enchondral Ossification

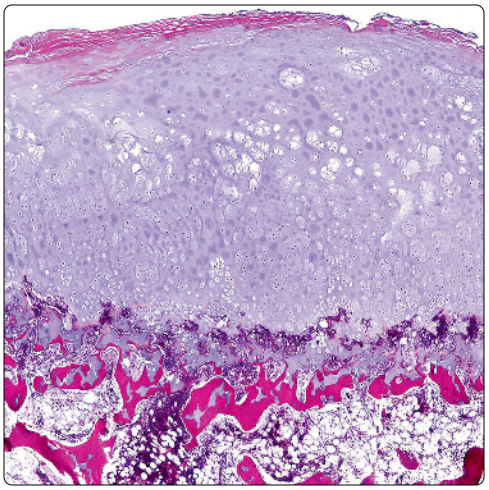


### Osteochondroma With Bifid Shape

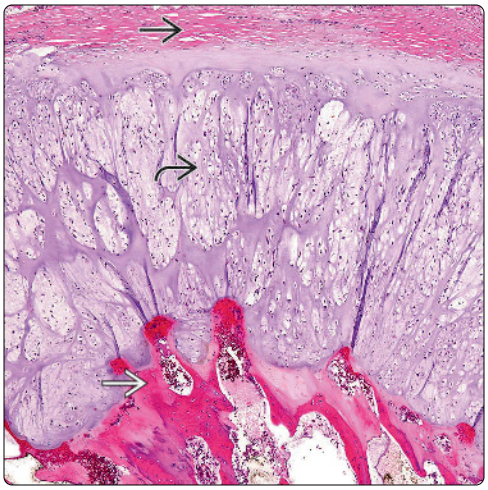


**(Left)** *This resected OCE has undergone complete enchondral ossification, a longstanding tumor. The surface consists of a thin shell of cortical-type bone and surrounds cancellous bone and fat.* **(Right)** *Whole-mount section of an OCE shows its bifid shape. Portions of the residual cartilage cap are present. The cartilage has undergone enchondral ossification, and the cancellous bone is surrounded by fatty marrow and bony stalk.*

### Cartilage Cap



### Cartilage Cap Resembling Growth Plate

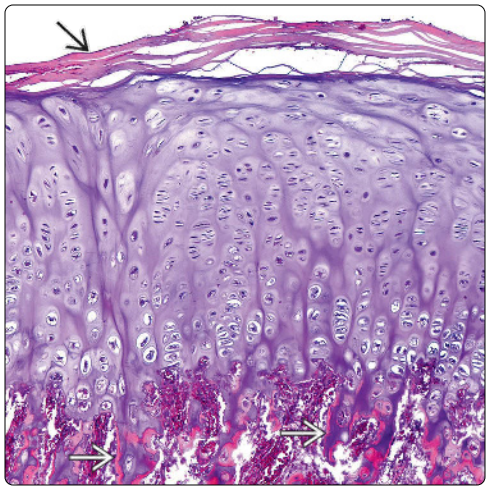


**(Left)** *Cartilage cap of OCE is covered by a fibrous periosteum. The cartilage undergoes enchondral ossification forming cancellous bone.* **(Right)** *Fibrous perichondrium overlies the cartilage cap of an OCE, and it mimics the zone of hypertrophy of the growth plate. The base of the cap is being sealed by bone, indicating cessation of growth.*

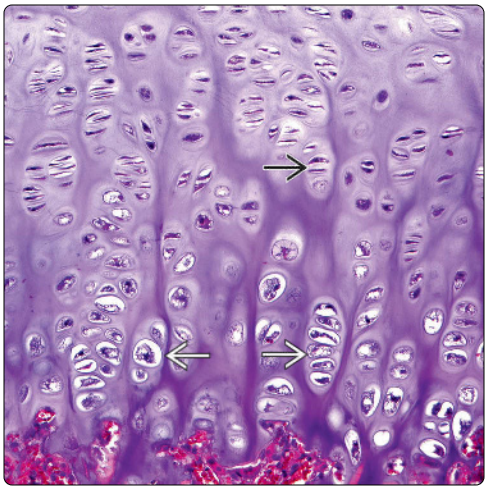


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**Perichondrium Overlying Cartilage Cap**

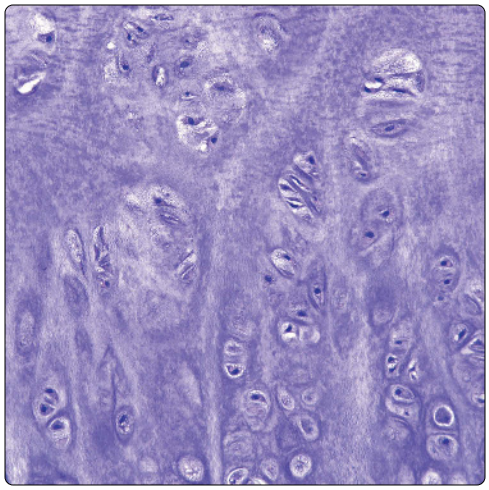


**Columns of Chondrocytes in Cap**

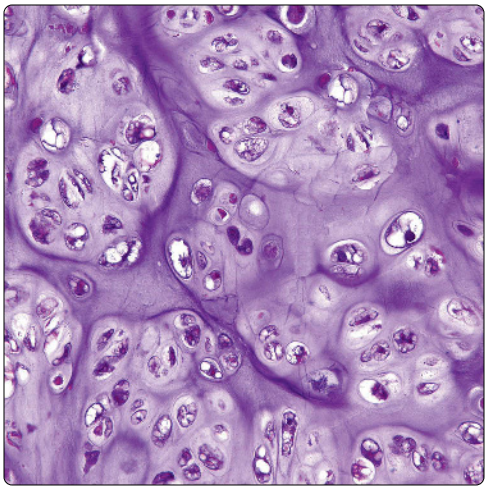


**(Left)** *Cartilaginous cap of an OCE is covered by a thin fibrous perichondrium. The cartilage mimics that of the growth plate and undergoes enchondral ossification, producing primary spongiosa-like structures, a feature of active growth.* **(Right)** *The chondrocytes in the cartilaginous cap are arranged in columns, a fashion that resembles growth plate cartilage. The chondrocytes enlarge and acquire more cytoplasm as they approach the base.*

**Chondrocytes Arranged in Columns**

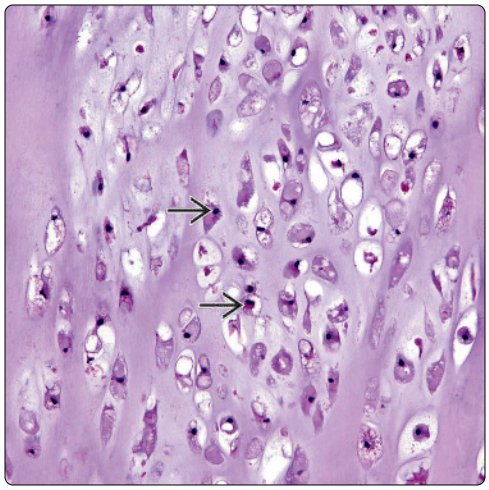


**Cellular Region of Cartilage Cap**

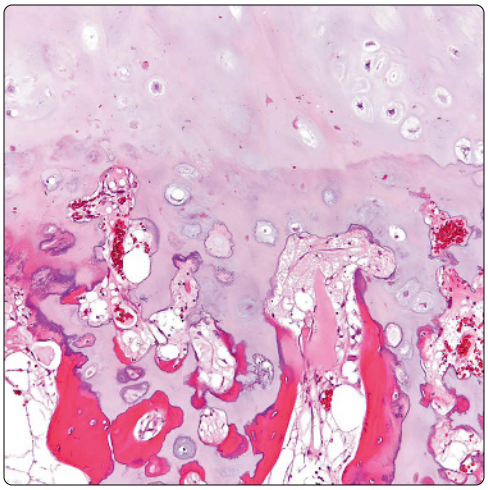


**(Left)** *Groups of chondrocytes are surrounded by abundant hyaline matrix in a cap of an OCE. The chondrocytes are arranged in a pattern that resembles growth plate-type cartilage. The chondrocytes have bland cytologic features.* **(Right)** *The cartilaginous cap of this OCE is cellular, and the chondrocytes are arranged in a disorganized pattern. The chondrocytes have small, round, and dark nuclei and show no significant cytologic atypia.*

**Cellular Portion of Cartilage Cap**



**Enchondral Ossification**

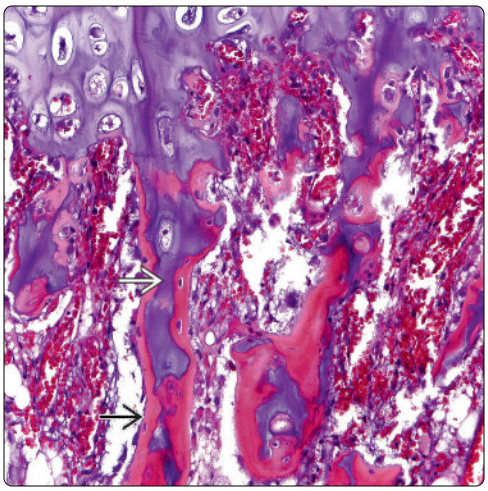


**(Left)** *Chondrocytes are arranged in a disorganized fashion in the cap of an OCE. There is abundant matrix, and the chondrocytes have small, round, dark nuclei and eosinophilic cytoplasm that has contracted away from the matrix.* **(Right)** *The base of an OCE shows the process of enchondral ossification. Portions of the cartilage cap is removed by osteoclasts and the residual struts act as templates for newly deposited bone.*

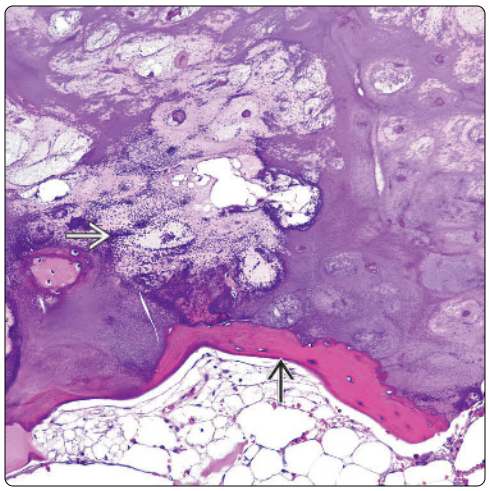


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### Primary Spongiosa-Like Tissue

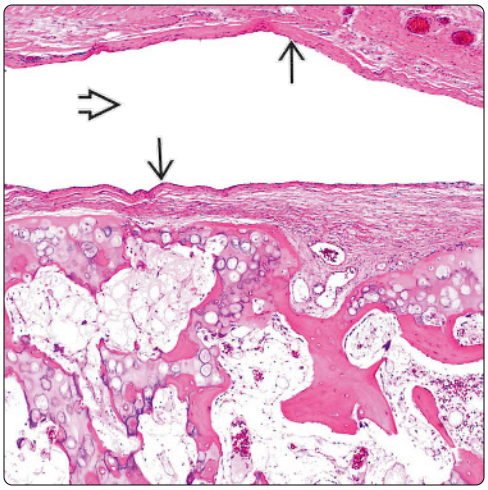


### Cessation of Active Growth

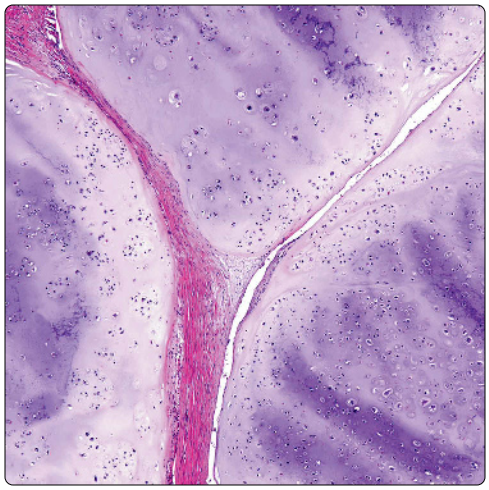


**(Left)** *The base of an actively growing OCE shows enchondral ossification. The features mimic the base of a growth plate with the production of primary spongiosa, consisting of cartilaginous cores ➡ of tissue sandwiched by layers of bone ⇨. (Right) Inactive OCE with a cartilage cap that has undergone extensive calcification ➡ is shown. The base has been sealed by a horizontally oriented bone ⇨.*

### Large Bursa

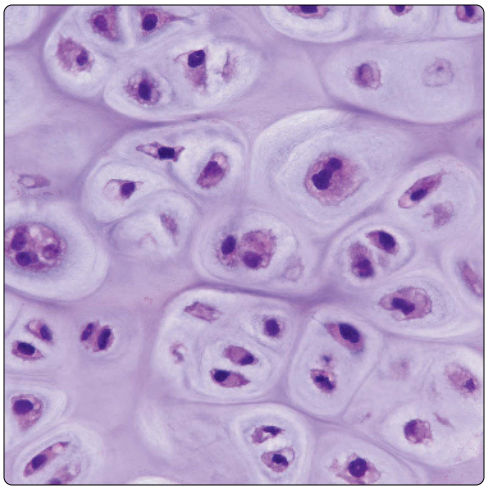


### Nodules Delineated by Fibrous Septum

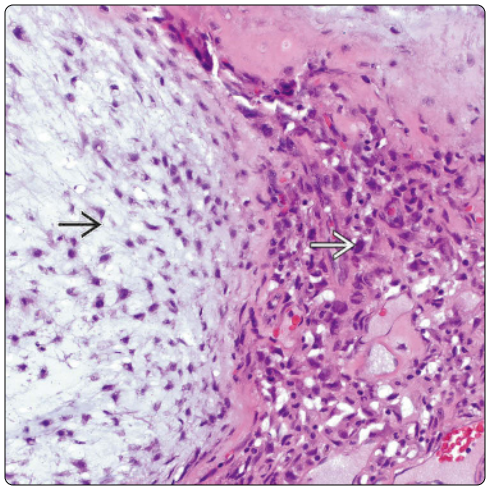


**(Left)** *A large bursa overlies the cartilage cap of an OCE; the majority of the cap has undergone enchondral ossification. The bursa is lined by synovium ⇨. The cavity ⇨ is filled with synovial fluid in vivo.* **(Right)** *Chondrosarcomatous component that arose in a large OCE consists of nodules of hypercellular hyaline cartilage. The nodules of cartilage are delineated by bands of fibrous tissue and do not exhibit the architecture of growth plate-like cartilage.*

### Atypical Chondrocytes



### Dedifferentiated Chondrosarcoma



**(Left)** *The chondrocytes in the hyaline CSA component of an OCE show cytologic atypia in the form of nucleomegaly, hyperchromasia, and multinucleation. These are the features of a grade 2/3 conventional-type CSA.* **(Right)** *Rarely does an OCE undergo malignant transformation into a dedifferentiated CSA. In this H&E, there is lobule of low-grade myxoid CSA ⇨ and a microscopic focus of pleomorphic spindle cell sarcoma ➡.*



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# Multiple Hereditary Osteochondromatosis

KEY FACTS

## TERMINOLOGY

- Hereditary multiple exostoses
- Autosomal dominant condition caused by mutations in 1 of the EXT genes
- ≥ 2 osteochondromas of juxtaepiphyseal region of long bones are required for diagnosis

## CLINICAL ISSUES

- 60% have positive family history of multiple osteochondromas
- Malignant transformation of osteochondroma to chondrosarcoma occurs in 0.5-5.0% of MHO patients
- Most patients are in their 2nd decade of life at time of diagnosis

## IMAGING

- Arises from surface of bone
- Cortices of lesion and underlying bone and their marrow cavities are in direct continuity

## MICROSCOPIC

- Similar to sporadic osteochondroma
- Peripheral cap of hyaline cartilage
- Malignant transformation should be suspected in cases with
  - Cartilage cap > 2 cm in thickness
  - Infiltration of preexisting bone
  - Nodular pattern with fibrous septa
  - Cartilage with mitotic figures and nuclear pleomorphism

## ANCILLARY TESTS

- Germline alterations in *EXT1* (located at 8q24) and *EXT2* (located at 11p11-p12) are involved in hereditary multiple osteochondromas

## TOP DIFFERENTIAL DIAGNOSES

- Surface (periosteal) chondroma
- surface (parosteal) osteosarcoma

**Multiple Osteochondromas**



*Multiple osteochondromas arising from the distal end of femur is shown. The osteochondromas grow in a direction away from the knee joint ⇨. Note the en face image of the osteochondroma on the anterior surface ⇨.*

**Multiple Osteochondromas**



*Two sessile osteochondromas arising from the distal end of femur in a patient with multiple hereditary osteochondromatosis ⇨ are shown. The cartilaginous cap is not visualized on plain radiograph and is best appreciated on an MR scan.*



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## TERMINOLOGY

### Abbreviations

- Multiple hereditary osteochondromatosis (MHO)

### Definitions

- Autosomal dominant condition caused by mutations in 1 of the EXT genes
- ≥ 2 osteochondromas of juxtaepiphyseal region of long bones are required for diagnosis

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - ~ 1 per 50,000 persons
  - Solitary (sporadic) osteochondromas are ≥ 6x more common than MHO
- Age
  - Most patients are in their 2nd decade of life at time of diagnosis
- Sex
  - Male preponderance

### Site

- Typically arises in appendicular skeleton
- Distal femur, proximal tibia, proximal humerus
- Can involve flat bones, such as ilium and scapula

### Presentation

- 60% have positive family history of multiple osteochondromas
- Multiple slowly enlarging firm lesions present for many years
- Painful

### Prognosis

- Malignant transformation of osteochondroma to chondrosarcoma occurs in 0.5-5.0% of MHO patients
  - Rarely, osteosarcoma and dedifferentiated chondrosarcoma have also been reported
- Patients may show deformities of forearm, inequality in limb length, varus or valgus angulation of knee, deformity of ankle, and disproportionate short stature

## IMAGING

### General Features

- Generally similar to sporadic osteochondroma
- Cortices of lesion and underlying bone and their marrow cavities are in direct continuity
- Cartilaginous cap is of varying thickness

## MACROSCOPIC

### General Features

- Generally similar to sporadic osteochondroma
- Outer layer consists of thin sheath of fibrous tissue that overlies pearly gray-white cartilaginous cap
- Cartilage cap of variable thickness, ranging from < 1 cm to several cm in depth
- Base of cartilage cap undergoes enchondral ossification and merges with areas that have appearance of cancellous bone

## MICROSCOPIC

### Histologic Features

- Similar to sporadic osteochondroma
- Peripheral cap of hyaline cartilage
  - Cellularity of cartilage decreases from deep to superficial layer
  - Chondrocytes are arranged in vague columns
- Chondrocytes exhibit minimal cytologic atypia and no mitotic activity
- Newly formed trabeculae at base of cartilage mimics primary spongiosa of normal growth plate
- Malignant transformation should be suspected in cases with
  - Cartilage cap > 2 cm in thickness
  - Infiltration of preexisting bone
  - Nodular pattern with fibrous septa
  - Cartilage with mitotic figures and nuclear pleomorphism
- Diagnosis of chondrosarcoma requires multidisciplinary approach

## ANCILLARY TESTS

### Genetic Testing

- Germline alterations in *EXT1* (located at 8q24) and *EXT2* (located at 11p11-p12) are involved in hereditary multiple osteochondromas
  - Loss of wild-type alleles has been reported in MHO and rare cases of sporadic osteochondroma
- Function of gene products of *EXT1* and *EXT2*
  - Proteins exostosin-1 (*EXT1* gene) and exostosin-2 (*EXT2* gene) are localized to endoplasmic reticulum and catalyze heparan sulphate polymerization
  - These 2 proteins are hypothesized to be essential for fibroblast growth factor and Indian hedgehog signaling within normal growth plate

## DIFFERENTIAL DIAGNOSIS

### Surface (Periosteal) Chondroma

- Composed of lobules of cartilage only, without endochondral ossification

### Surface (Parosteal) Osteosarcoma

- Anchored to external surface of cortex without continuity between medullary cavity and center of mass
- Parosteal osteosarcoma contains spindle-shaped malignant cells adjacent to neoplastic bone

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3. Ahmed AR et al: Secondary chondrosarcoma in osteochondroma: Report of 107 patients. Clin Orthop 411:193-206, 2003

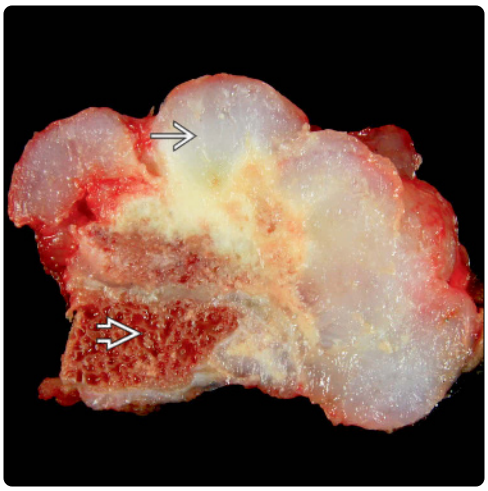



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**Multiple Hereditary Osteochondromatosis**

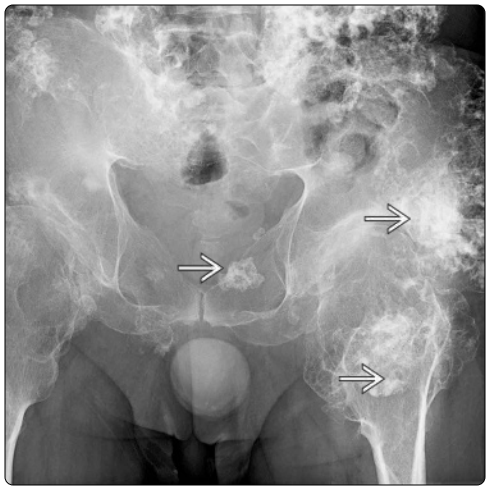


**Thickened Cartilage Cap**

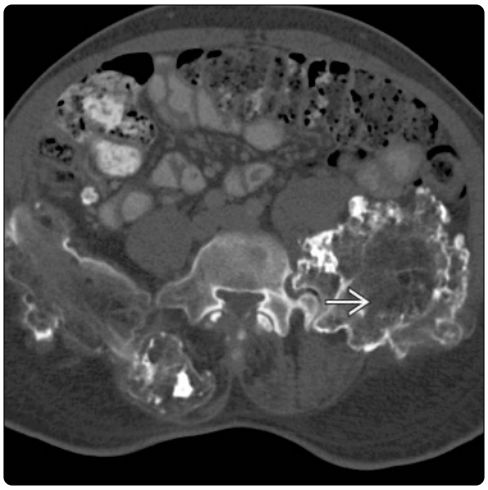


**(Left)** *The surface of a 7-cm osteochondroma is shown. The surface is covered by a 0.2-cm layer of cartilage. An osteochondroma with a thin cartilaginous cap is unlikely to be associated with malignant degeneration.* **(Right)** *A markedly thickened bluish-grey cartilaginous cap measuring 2.1 cm is shown. The cartilage does not infiltrate the underlying cancellous bone. Although concerning for chondrosarcoma, in isolation, this finding is not diagnostic for malignant transformation.*

**Multiple Osteochondromas**

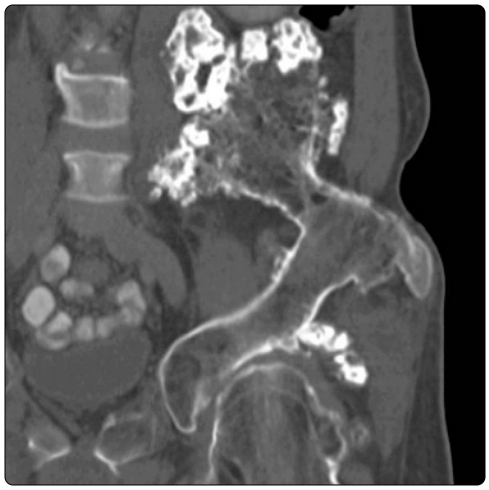


**Multiple Osteochondromas**



**(Left)** *Multiple hereditary osteochondromatosis is seen. Multiple heavily mineralized osteochondromas are seen involving the proximal femur and pelvis.* **(Right)** *Axial CT scan of multiple hereditary osteochondromatosis shows multiple osteochondromas involving the iliac bones. The host cancellous bone extends into the osteochondroma, a feature that distinguishes this lesion from other surface cartilaginous lesions. The subchondral region is heavily mineralized. The cartilaginous cap is not well visualized.*

**Multiple Pelvic Osteochondromas**



**Malignant Transformation.**

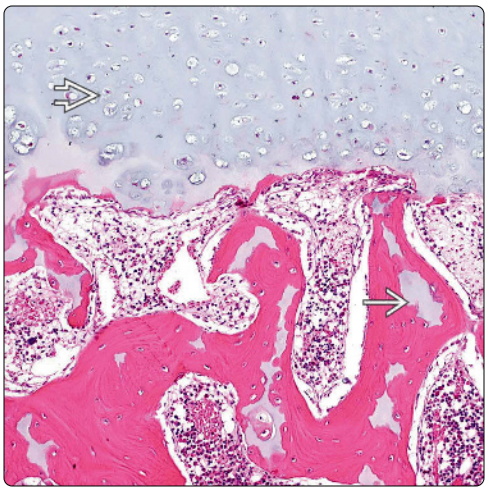


**(Left)** *Coronal CT shows multiple osteochondromas involving the iliac bone. The host cancellous bone extends into the osteochondroma. The subchondral region of the osteochondroma is heavily mineralized.* **(Right)** *This large sessile osteochondroma involving the iliac bone has undergone malignant transformation. The underlying osteochondroma is heavily mineralized. The large extraosseous lesion was resected and represented a grade 1 chondrosarcoma.*

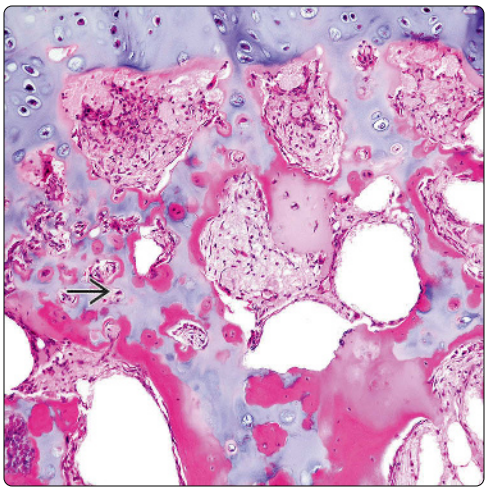


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### Cartilaginous Cap

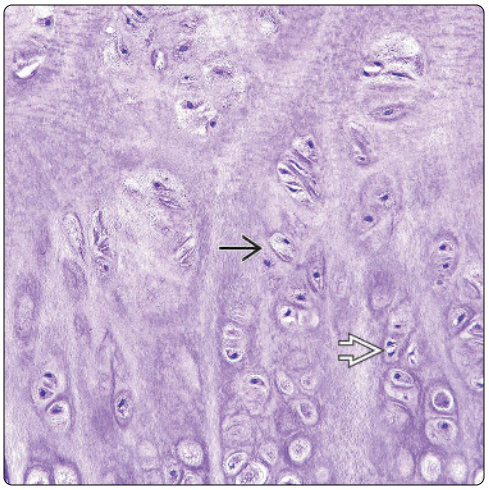


### Endochondral Ossification

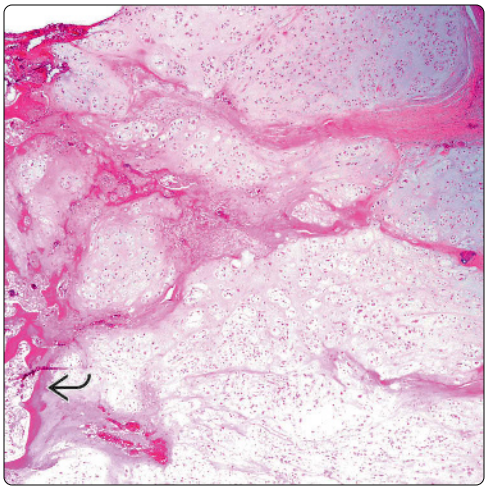


**(Left)** *The cartilaginous cap of this osteochondroma is composed of hyaline cartilage. The increased cellularity of the cartilage, particularly in an actively growing skeleton, does not raise concern for malignancy. The cartilage is seen to undergo endochondral ossification.* **(Right)** *The cartilaginous cap is composed of hyaline cartilage. The cartilage is seen to undergo endochondral ossification, producing a primary spongiosa-like appearance. This is a feature seen in a growing skeleton.*

### Cartilaginous Cap of Osteochondroma

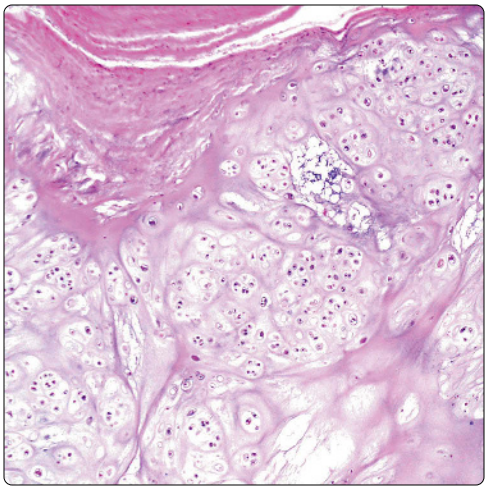


### Malignant Transformation

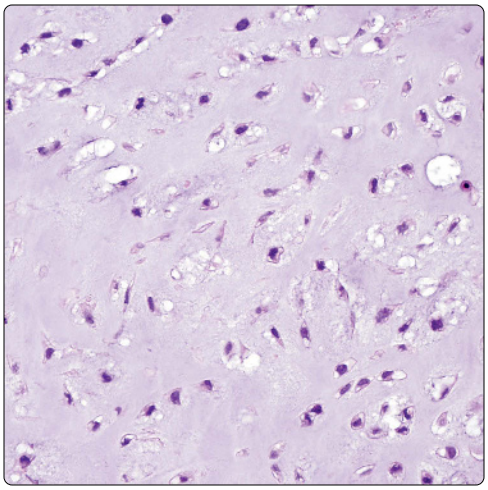


**(Left)** *This histologic image is from the cap of an osteochondroma. The columns of chondrocytes mimic the zone of hypertrophy of the growth plate. The binucleated chondrocytes should not raise concern for malignant change.* **(Right)** *Chondrosarcoma arising from an osteochondroma is shown. Note the base of the preexisting osteochondroma. The lobulated architecture is a histologic feature of a chondrosarcoma arising from an osteochondroma. Also note the increased tumor cellularity.*

### Malignant Degeneration



### Chondrosarcoma



**(Left)** *In this H&E of chondrosarcoma arising in osteochondroma, the osteochondroma is not seen. The neoplasm shows increased cellularity. The lobules of cartilage were separated by fibrous septa.* **(Right)** *This H&E shows a chondrosarcoma. The biopsy shows hypercellular cartilage. A low-grade chondrosarcoma may be difficult to distinguish from an osteochondroma on needle biopsy.*



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# Enchondroma

KEY FACTS

## TERMINOLOGY

- Common benign primary bone tumor that accounts for 3-10% of all bone tumors

## CLINICAL ISSUES

- Usually presents during 3rd and 4th decades of life
- Almost 90% of enchondromas (enchondromas) are solitary
- Predominate in distal appendicular skeleton
- Commonly asymptomatic
- Frequently detected as incidental finding
- Solitary enchondromas can be followed
- Tumors with questionable radiographic findings should be curetted to rule out low-grade chondrosarcoma

## IMAGING

- Spherical or oblong lucent lesion
- Well-defined margins
- Radiodensities with dense speckled pattern and "arcs & rings"
- In children enchondromas tend to be larger, show endosteal scalloping & rare mineralization

## MACROSCOPIC

- Range in size from 3-5 cm
- Some large enough to produce visible deformities
- Pearly white or gray glistening
- Nodular architecture ± endosteal scalloping

## MICROSCOPIC

- Composed of cartilaginous nodules
- Well circumscribed with no infiltration of trabecular bone
- Matrix is hyaline
- Myxoid matrix is uncommon
- Enchondromas in digits and in setting of Ollier disease & Maffucci syndrome may be more cellular and demonstrate cytologic atypia
- Myxoid change and chondrocyte necrosis should raise suspicion of low-grade chondrosarcoma

**Rings & Arcs Pattern**



*Enchondroma arising in the diaphysis of the tibia demonstrates classic rings & arcs pattern corresponding to reactive bone rimming individual nodules of cartilage. Spiculated radiodensities represent calcifications of the hyaline matrix. There is focal scalloping of the cortex.*

**Blue-Gray Nodules**



*An enchondroma arising in the proximal humerus is shown. The tumor is oval, gray-blue, and glistening, and it is well delineated from the surrounding trabecular bone. The white area in the center represents endochondral ossification of the tumor.*



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## TERMINOLOGY

### Synonyms

- Chondroma of bone

### Definitions

- Benign primary bone tumor composed of chondrocytes producing cartilage matrix arising within medullary cavity

## ETIOLOGY/PATHOGENESIS

### Unknown

- Likely results from genetic events in stem cells

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Common primary bone tumor
    - 2nd in frequency to osteochondroma
  - Accounts for ~ 12-24% of primary benign bone tumors
  - Represents 3-10% of all primary bone tumors
- Age
  - Usually presents during 3rd to 4th decades of life
  - Uncommon in children and elderly
- Sex
  - Equal gender distribution
- Ethnicity
  - No racial predilections

### Site

- Arise only in bones that form from process of enchondral ossification during embryologic development
  - Does not develop in bones that are intramembranous in formation
- Almost 60% of solitary enchondromas arise in small tubular bones of hands and feet
  - Represents most common primary bone tumor of hand
- Other frequent sites of involvement include long tubular bones (20-45%)
  - Frequently affected bones are femur, tibia, humerus, fibula
    - Usually arises in metaphysis and proximal and distal potions of diaphysis
- Uncommon for enchondromas to arise in flat bones & spine
  - < 3% develop in pelvis
  - Vast majority of cartilage tumors arising in pelvis are chondrosarcomas

### Presentation

- Vast majority are asymptomatic
- Frequently detected as incidental finding during investigation of other conditions
  - Relatively common for enchondroma to be diagnosed in patients with pain associated with other disorders, such as osteoarthritis, torn menisci, and rotator cuff and metastatic carcinoma
    - Pain is erroneously attributed to enchondroma in periarticular bone
- ~ 90% of enchondromas are solitary
- Slow growing
  - May show no growth in adulthood
  - Growth may occur over many years
- Infrequently painful except if there is pathological fracture
  - Pain caused by generation of microfractures
  - Painful intraosseous hyaline cartilage tumor should raise possibility of chondrosarcoma
- Fractures most commonly affect tumor located in phalanges
  - Large tumors in long bones rarely present with dramatic pathologic fracture

### Natural History

- Slow, limited growth that eventually ceases
- Multiple lesions occur in several syndromes including
  - Ollier disease
    - ≥ 2 enchondromas
  - Maffucci syndrome
    - ≥ 2 enchondromas and soft tissue hemangiomas
      - Most common vascular tumor is spindle cell hemangioma
  - Metachondromatosis
    - ≥ 2 enchondromas and osteochondromas
    - Autosomal dominant mode of inheritance
    - Caused by loss of function of *PTPN11* gene
- Malignant transformation of isolated lesion into chondrosarcoma uncommon
  - Increased incidence of malignant transformation in enchondromatoses
  - Not uncommon to see area with histologic features of enchondroma in chondrosarcoma

### Treatment

- Most asymptomatic solitary enchondromas can be followed clinically and with appropriate imaging studies
- Determination of which tumor should be operated on depends on clinical circumstances
  - Painful tumors may require therapy to alleviate symptoms and to exclude low-grade chondrosarcoma
  - Tumors with radiographic findings that raise suspicion of chondrosarcoma should be biopsied or curetted
    - Prominent areas of lucency, deep cortical erosions, marrow edema may raise suspicion
  - Some patients may require treatment for psychological reasons
  - Large tumors (> 5 cm in greatest dimension) should be viewed with caution
- Surgical treatment is usually aggressive thorough curettage, adjuvant added to intraosseous defect and packing with bone graft or cement
- En bloc resection is performed on sizable lesions in expendable bones, such as proximal fibula or rib
- If needle or open biopsy is performed should target lucent component

### Prognosis

- Local recurrence following curettage is very common (3-4%)
  - Results from continued growth from cartilage not removed
- Local recurrence should raise suspicion of low-grade chondrosarcoma



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- Small percentage of enchondromas may undergo biological progression to conventional and dedifferentiated chondrosarcoma
  - True incidence of this phenomenon is unknown as frequency of enchondroma is undetermined

## IMAGING

### Radiographic Findings

- Spherical or oblong in shape
- Most tumors are lucent with scattered areas of increased radiodensity
  - Extent of mineralization varies considerably
  - Many tumors contain scattered, dense, stippled opacities
  - Represent irregular calcification of cartilaginous matrix
    - Mineral is calcium hydroxy apatite
  - Rim of mineralized reactive bone surrounding individual radiolucent nodules of cartilage produce arcs, "O" or "C" ring-like mineralized structures
    - Bone forms from both enchondral ossification of neoplastic cartilage or intramembranous ossification in response to tumor
  - Progressive mineralization may occur over time and can be mistaken for enlargement of tumor
  - In older tumors, mineralized nodules coalesce and form solid, stone-like intraosseous density
    - Focal loss of calcification over time may indicate malignant transformation
- Well-defined margins
  - Margins may or may not be associated with sclerosis
- Tumor adjacent to inner cortex produces scalloping
  - Scalloping has smooth contours and can be superficial and sometimes deep
- Large tumors in small or flat bones can cause marked thinning of cortex or cortical resorption
- Progressively enlarging tumors in small & flat bones can cause significant expansion of bone
  - Marked asymmetric bone expansion is uncommon and known as enchondroma protuberans
- Cortical thinning, bone expansion and periosteal reaction in combination are usually harbingers of malignancy when associated with cartilage tumors in flat or large tubular bones
- Periosteal reaction usually absent unless fracture has occurred
- No soft tissue extension or mass

### MR Findings

- High signal intensity on T2-weighted images
- Low to intermediate signal intensity on T1-weighted images
- Mineralized cartilage produces signal void
- Marrow surrounding tumor is usually normal, except if there has been fracture
  - Presence of surrounding marrow edema raises possibility of chondrosarcoma

### CT Findings

- Well-circumscribed, lobulated tumor
- Stippled calcifications
- Arcs, rings, and C-shaped patterns of mineralization
- Scalloped endosteum with cortical thinning
- No periosteal reaction unless associated with fracture

### Bone Scan

- May be negative
- Actively calcifying tumors show moderate activity
- Fractured tumors show marked activity

### PET Scan

- Enchondroma has SUV of < 2 with F-18 FDG PET
  - High SUV is worrisome for chondrosarcoma

## MACROSCOPIC

### General Features

- Firm to hard
  - Grittiness depends on amount of matrix mineralization & reactive bone formation
- Composed of coalescing pearly white or gray nodules that are usually 3-5 mm in diameter
  - Gray glistening nodules of hyaline cartilage
  - White areas represent mineralized matrix
- Scalloping of endosteal surface may be present
- Located in medullary cavity
- Well demarcated from surrounding bone
  - Eccentrically positioned tumor can cause prominent scalloping

### Sections to Be Submitted

- Process entire tumor in curettage specimen
- Resections: Minimum of 1 section per cm
  - Concentrate on noncalcified regions
  - Submit closest bone and soft tissue margins
  - Sample interface between tumor and surrounding bone in order to exclude infiltrative growth pattern, which is seen in low-grade chondrosarcoma
- Process some tumor without decalcification for molecular analysis if needed

### Size

- Relatively small; ranges from 1-5 cm
- Tumors in small bones may cause deformity of bone
- Uncommon for tumor in long bone to be large enough to produce visible distortion

## MOLECULAR

### Mutations

- *IDH1*/*IDH2* mutations identified in > 50% of enchondromas
  - Are also identified in chondrosarcomas and therefore cannot be used to distinguish enchondroma from low-grade chondrosarcoma
  - Mutation results in generation of oncometabolite D-2-hydroxyglutarate
- *IDH1*/*IDH2* mutations present in conventional chondrosarcoma, dedifferentiated chondrosarcoma, and spindle cell hemangioma

## MICROSCOPIC

### Histologic Features

- Composed of variably sized nodules of hyaline cartilage
  - Fibrocartilage differentiation is rare, elastic cartilage differentiation does not occur



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- Nodules of cartilage well circumscribed and have sharp margin with surrounding bone
- Cartilage is hypo- to moderately cellular
- Contains chondrocytes that have uniform, small, round, hyperchromatic (lymphocyte-like) nuclei
- Occasionally, cells are binucleate and have fine chromatin and small nucleolus
- Matrix is usually hyaline type
  - Most prominent component of lesion
- Myxoid matrix is uncommon and when present is focal
  - Prominent myxoid component should raise suspicion for chondrosarcoma
- Hyaline matrix frequently calcifies
  - Calcification appears as amorphous purple or basophilic granular material; chondrocytes undergo necrosis in zones of calcification
- Periphery of nodules often undergo enchondral ossification
  - Trabecular bone rims periphery of nodules of cartilage
  - No encasement of preexisting trabecular bone (infiltration), which is feature of chondrosarcoma
  - At periphery of tumor, remnants of cartilage may be in center of broad bony trabeculae
- Enchondromas arising in digits frequently hypercellular and demonstrate mild cytologic atypia
- Enchondromas in Ollier disease and Maffucci syndrome may be hypercellular and exhibit cytologic atypia, and matrix may be focally myxoid

## ANCILLARY TESTS

### Immunohistochemistry

- Chondrocytes strongly express vimentin and S100

### Genetic Testing

- Abnormalities involving chromosomes 5, 6, 7, 12, & 17

## DIFFERENTIAL DIAGNOSIS

### Low-Grade Chondrosarcoma

- Grows with infiltrative pattern
- Greater degree of cellularity and nuclear atypia
- Recent study has shown increased expression of 2 microRNAs, miRs-181a and -138, in low-grade chondrosarcomas compared with enchondromas
- Treatment of low-grade chondrosarcoma and enchondroma in long bones is usually same
  - Both treated with aggressive curettage
- In latest World Health organization (WHO) classification, "atypical cartilaginous tumor/chondrosarcoma grade I" suggested for problematic low-grade tumors
- ERG immunohistochemical stain has been reported to demonstrate positive nuclear immunohistochemical stain in chondrosarcoma but usually not in enchondroma

### Chondromyxoid Fibroma

- Contains myxoid and fibrous elements
- Lacks well-formed hyaline cartilage

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Well-circumscribed tumor composed of nodules of hyaline cartilage; cartilage hypo- to moderately cellular
- Chondrocytes cytologically banal

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**Plain Radiograph**



**Rings & Arcs**

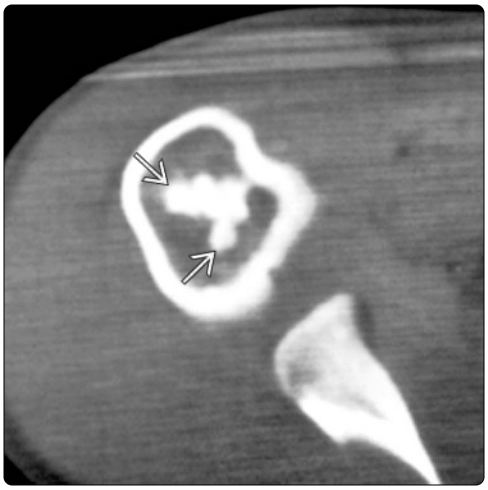


**(Left)** *AP radiograph of the distal femur shows a well-defined lytic enchondroma surrounded by a faintly sclerotic boundary & containing internal popcorn-like radiodensities. "Arc & ring" radiodensities are also present.* **(Right)** *Axial CT scan through enchondroma demonstrates discrete "rings & arcs". The noncalcified parts of the tumor have a very low density. The entire tumor is demarcated by a thin, sclerotic wall indicating its noninvasive nature.*

**Calcified Enchondroma**



**Clusters of Grapes**



**(Left)** *In this radiograph of a heavily calcified enchondroma in the proximal humerus, the uniform distribution of the calcifications suggests that no portion of the tumor is actively growing. Well-formed, arc-like patterns of mineralization are present. The cortex is unremarkable.* **(Right)** *Axial CT scan through an enchondroma shows individual nodules that are densely mineralized. The nodular architecture can be discerned from the "cluster of grapes" morphology.*

**T1 MR**



**T2 MR**



**(Left)** *T1-weighted MR shows a well-defined, low-intensity medullary tumor of the distal femur. The lesion has well-defined, lobulated margins and therefore is probably noninvasive. The tumor thins and scallops the posterior cortex, and there is no periosteal reaction or peritumoral edema.* **(Right)** *Enchondroma has high signal intensity on T2 MR indicative of its high water content. The tumor scallops the posterior cortex, a common finding in eccentric enchondromas.*



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**Low-Signal Enchondroma on T1 MR**



**High-Signal Enchondroma on T2 MR**

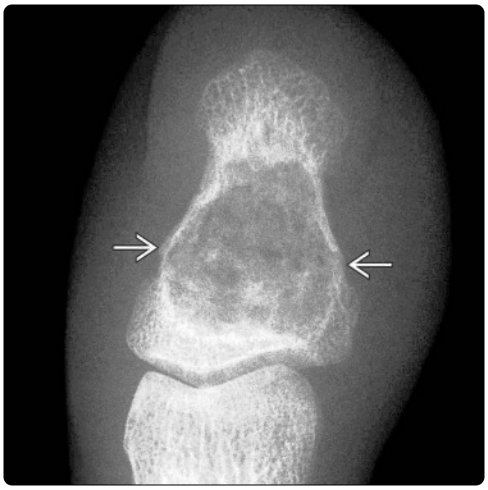


**(Left)** *T1-weighted MR of enchondroma shows its low signal intensity & well-delineated lobular margins ⇨. The bright signal within the lesion could represent either marrow fat trapped between cartilage nodules or fat within enchondral bone formed by the tumor.* **(Right)** *T2-weighted MR of the same enchondroma ➡ shows its nodular structure. The target-like appearance of the nodules is probably the result of high-signal cartilage nodules containing internal low-signal calcifications.*

**Enchondroma of Finger**

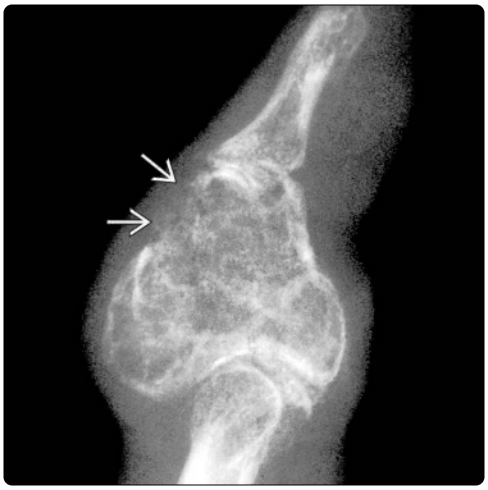


**Enchondroma of Terminal Phalanx**

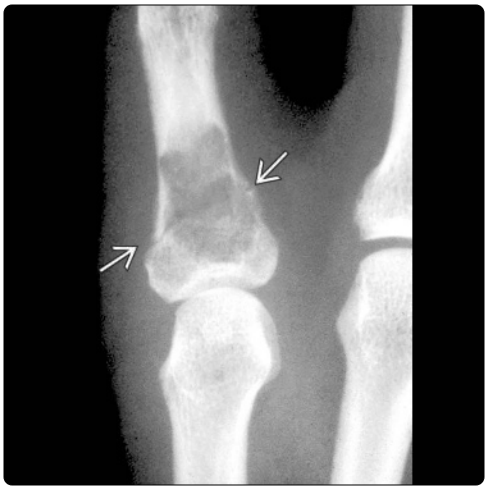


**(Left)** *A typical enchondroma of the proximal phalanx of the 3rd finger ➡ is lytic, has well-circumscribed margins, and causes mild expansion of the bone. Mineralization is somewhat less prevalent in enchondromas of the digits.* **(Right)** *An enchondroma is seen involving the terminal phalanx of a toe. Note that cortical erosion has lead to moderate expansion ➡ of the bone. This is a common feature of enchondromas in the digits & should not be taken as evidence of malignancy.*

**Large Enchondroma of Finger**



**Enchondroma of Finger With Fracture**

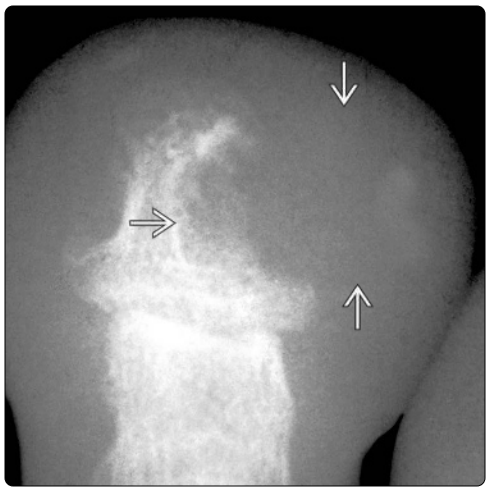


**(Left)** *An extreme example of expansion due to a benign enchondroma is shown. Notice that the phalanx appears shortened, most likely indicating a pathological fracture. In areas, the cortex is absent & is replaced by a thin layer of periosteal reactive bone ➡.* **(Right)** *A typical enchondroma of a proximal phalanx is shown with a pathological fracture ➡. The lytic tumor has well-circumscribed margins & has scalloped & thinned the cortex, making it vulnerable to breakage.*

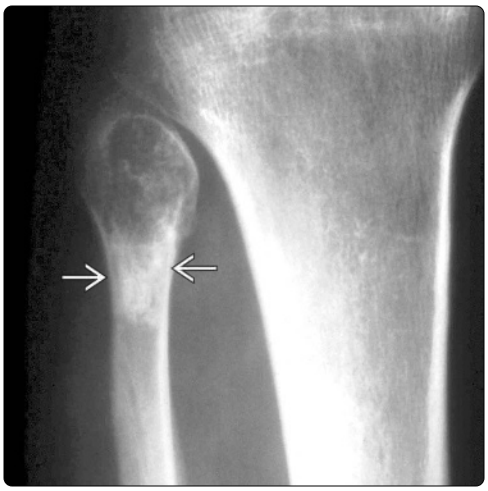


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### Eccentric Enchondroma

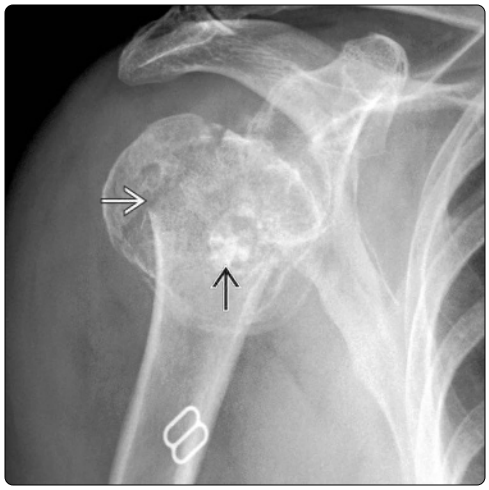


### Densely Mineralized Enchondroma



**(Left)** *Radiograph shows a well-defined, eccentric lytic enchondroma of the terminal phalanx that extends into soft tissues. The diagnosis of chondroma cannot be made with certainty from imaging.* **(Right)** *A densely mineralized enchondroma of the proximal fibula is shown. Nodules and rings & arcs are difficult to appreciate from the plain radiograph. The cortex is intact.*

### Enchondroma With Fracture



### Pathologic Fracture

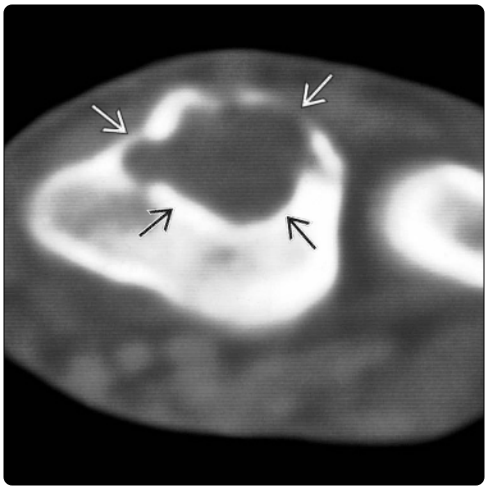


**(Left)** *Proximal humerus is shown with a fracture near an enchondroma. The appearance suggests a typical osteoporotic fracture, although proximity to the enchondroma raises the question of its role in the break.* **(Right)** *CT scan through the fractured humerus shows that the fracture line does not go through the enchondroma, and the tumor has not caused cortical thinning. This indicates that the fracture was not caused by the enchondroma and is an incidental finding.*

### Enchondroma of Distal Radius



### CT of Enchondroma of Distal Radius



**(Left)** *Radiograph shows enchondroma of the epiphysis of distal radius; epiphysis is an unusual location. The lytic tumor is well circumscribed, has a scalloped sclerotic margin, and extends to the subchondral bone region.* **(Right)** *Axial CT shows an enchondroma of the distal radius. The low-intensity tumor has well-circumscribed, lobulated, sclerotic margins. In areas, the tumor has produced endosteal scalloping & thinning of the cortex.*



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**Enchondroma of Epiphysis**

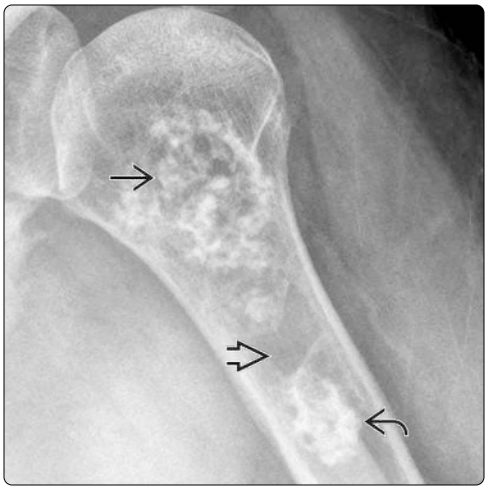


**CT of Epiphyseal Enchondroma**



**(Left)** *Radiograph shows an enchondroma of the femoral head, an unusual location for enchondroma, & the differential diagnosis includes chondroblastoma. The subtle tumor is well circumscribed, predominately lytic, & contains small, ring-like radiodensities* ➡. **(Right)** *Enchondroma of epiphysis of the femoral head* ➡, *an unusual location for this type of tumor, is shown. The demarcated tumor is dark with scattered internal ring-like & irregular spicules of mineralization.*

**Enchondroma of Humerus**

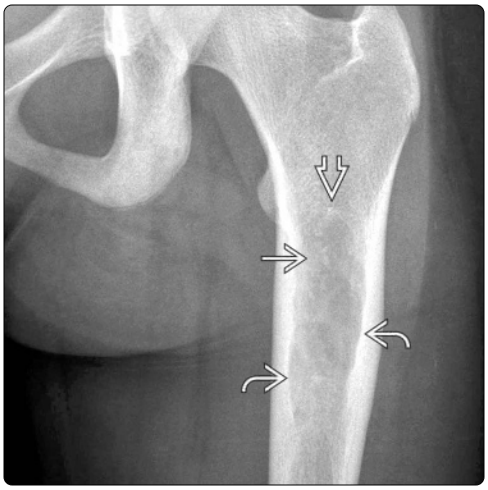


**Radiograph of Large Enchondroma**



**(Left)** *Enchondroma arising in the proximal humeral shaft demonstrates fairly well-mineralized proximal* ⇨ & *distal* ⇨ *portions of the tumor with an intervening nonmineralized area* ⇨. **(Right)** *A long, well-mineralized enchondroma involving the proximal and mid humeral shaft is shown. There is endosteal resorption, cortical thinning, and mild expansion of the bone. No periosteal reaction or soft tissue mass is identified. The uniform mineralization suggests the dormant condition of this lesion.*

**Enchondroma Arising in Child**



**Enchondroma of Tibial Epiphysis**



**(Left)** *Enchondroma of the femur* ➡ *arising in a 15 year old is shown. A lobulated, lucent lesion involves the diaphysis of the femur. There is endosteal scalloping* ➡ & *scant mineralization. The tumor is well demarcated with a thin, sclerotic rim proximally* ➡. **(Right)** *Enchondroma involving the epiphysis and focally extending into the metaphysis* ➡ *is shown. The tumor is dark and well demarcated on this MR. It is unusual for enchondromas to predominantly involve the epiphysis of long tumor bones.*

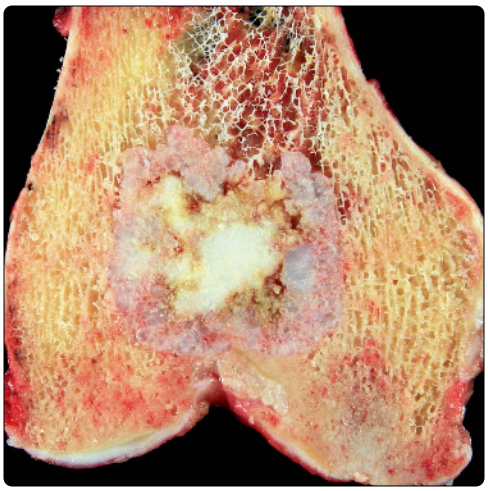


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**Enchondroma of Calcaneus**

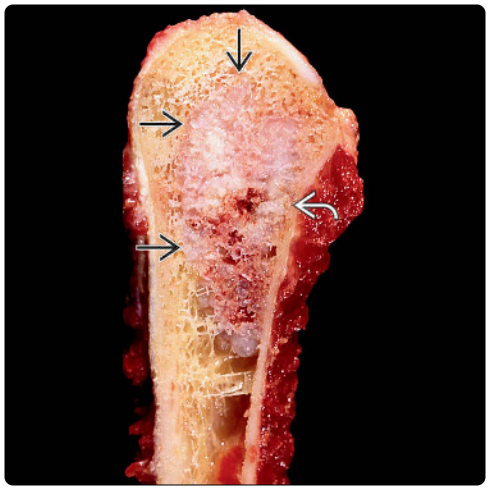


**Mineralized Enchondroma of Distal Femur**



**(Left)** *Enchondroma arising in the calcaneus is shown. This is an unusual location for an enchondroma. On this T2 MR, the tumor shows high signal intensity, is lobulated and well demarcated from the surrounding bone.* **(Right)** *Well-circumscribed enchondroma shows that the tumor is composed of nodules of cartilage that vary in size and are gray-blue and glistening. The tan-white regions represent foci of matrix calcification.*

**Enchondroma of Fibula**

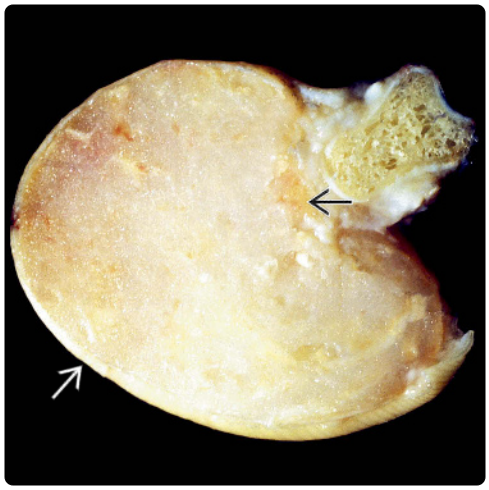


**Enchondroma Protuberans**

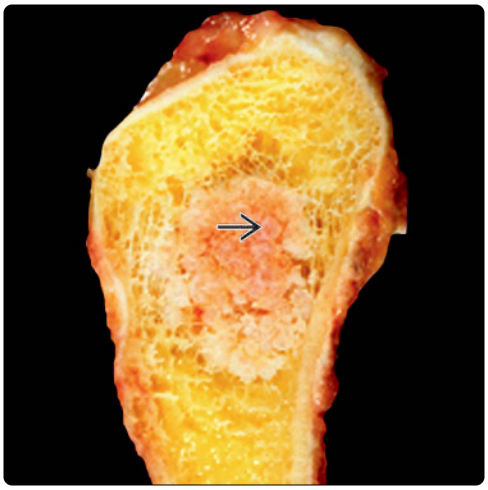


**(Left)** *Resected proximal fibula contains a well-circumscribed enchondroma that spans the proximal diaphysis to the distal portion of epiphysis. The gray-tan-white tumor is composed of multiple nodules, which focally abut the endosteum. The cortex is intact.* **(Right)** *Enchondroma protuberans of distal phalanx caused marked deformity of the end of the toe. The tumor manifests as a large, eccentric mass that has resulted in distortion of the lateral aspect of the nail. The overlying skin shows focal ulceration.*

**Enchondroma Protuberans**



**Resected Enchondroma**

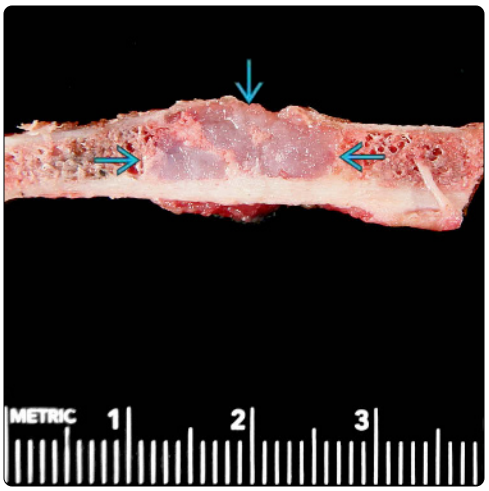


**(Left)** *An amputated distal toe contains a large enchondroma protuberans. The solid, gray-tan tumor has replaced much of the phalanx with a small proximal portion preserved. The overlying skin is intact.* **(Right)** *Enchondroma of fibula is well circumscribed & does not involve the cortex. It is composed of multiple nodules of gray glistening and pearly white hyaline cartilage. Some of the nodules are rimmed by a thin layer of white tissue, which represents reactive bone.*

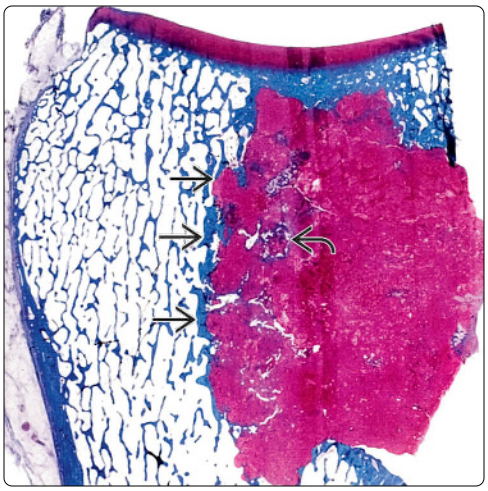


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### Enchondroma of Pubic Bone

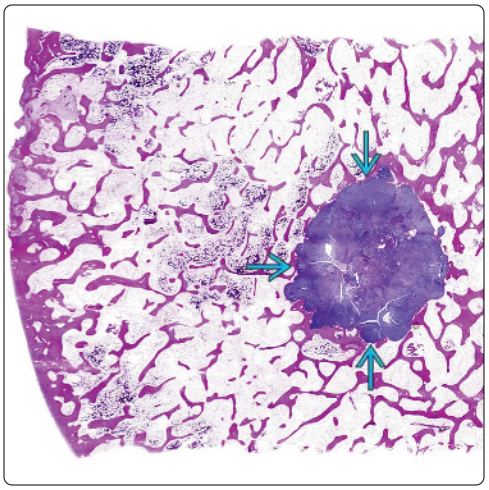



### Sclerotic Margin

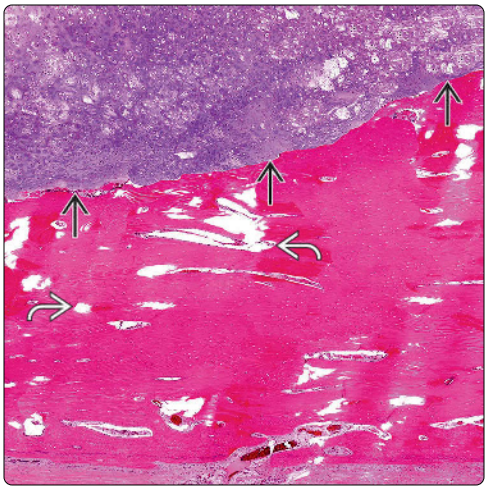


**(Left)** *Enchondroma is shown arising in the pubic bone, which is a very unusual location as the vast majority of pelvic cartilage tumors are chondrosarcomas. The tumor is gray glistening, lobulated, and well circumscribed.* **(Right)** *Goldner trichome stain shows a magenta-colored enchondroma in the proximal fibula. The tumor has a somewhat irregular but well-delineated margin that is bordered by sclerotic bony trabeculae. Some of the neoplastic cartilage has undergone enchondral ossification.*

### Incidental Enchondroma

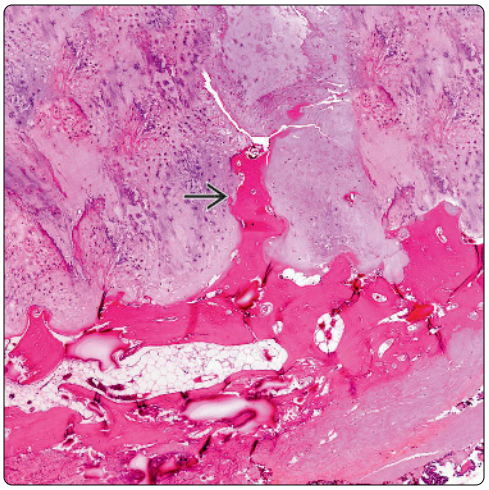


### Periphery of Enchondroma

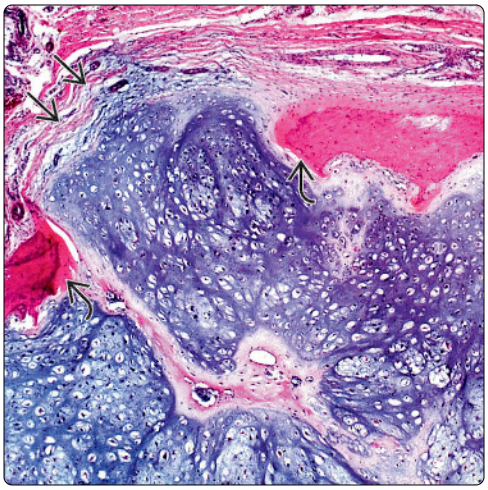


**(Left)** *A small, incidental enchondroma found in a femoral head resected for severe osteoarthritis is shown. The enchondroma is lobulated and does not demonstrate an infiltrative growth pattern.* **(Right)** *Enchondroma abuts the inner surface of the cortex and has produced a gentle scallop of its contour. The tumor is well circumscribed and does not infiltrate the haversian systems of the cortex.*

### Periphery of Enchondroma



### Enchondroma Eroding Cortex

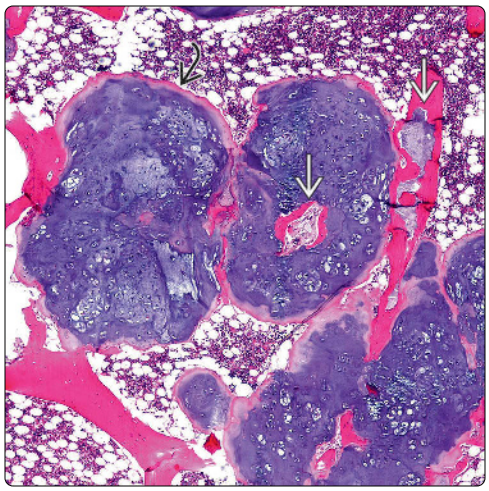


**(Left)** *Peripheral, well-delineated margin of an enchondroma is shown adjacent to the endosteum. A trabeculum of bone extends into the tumor. A section through this trabeculum perpendicular to the plane could mimic an infiltrative growth pattern with tumor completely surrounding the bone.* **(Right)** *Peripheral aspect of a digital enchondroma shows tumor eroding the cortex and bulging into the overlying periosteum. This type of local aggressive growth is often seen in the digits.*



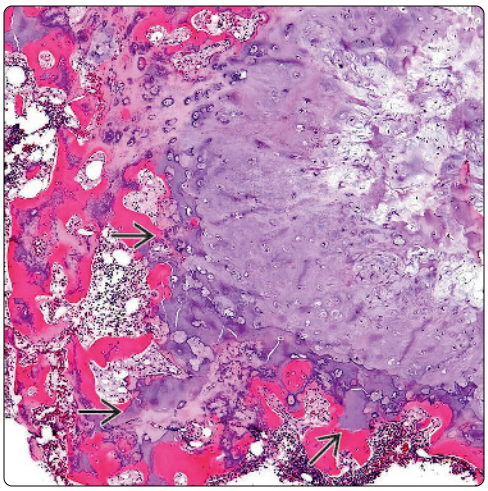
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### Multiple Nodules of Enchondroma

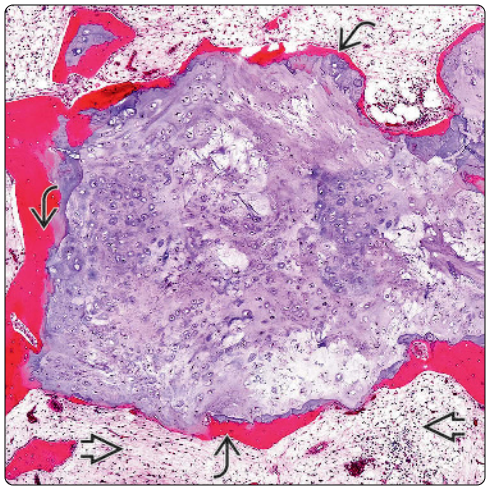


**(Left)** *Multiple nodules of an enchondroma are seen growing in the medullary cavity of the bone. The well-circumscribed nodules are encased by a thin rim of reactive bone. Portions of the neoplastic cartilage have undergone enchondral ossification & remain in the centers of some trabeculae.* **(Right)** *The edge of an enchondroma undergoes active enchondral ossification. The mineralized cartilage is resorbed by osteoclasts with persistent portions acting as scaffolding for the deposition of bone.*

### Enchondral Ossification

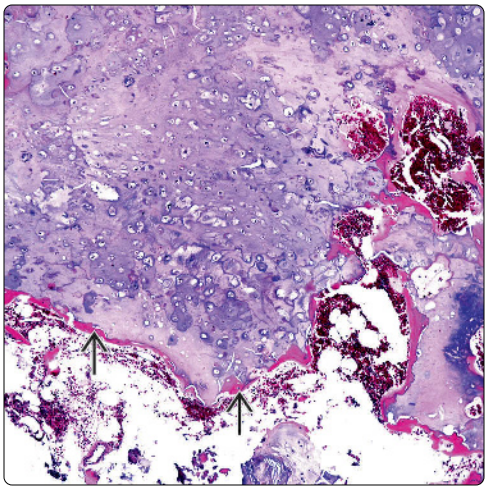


### Rimmed by Reactive Bone

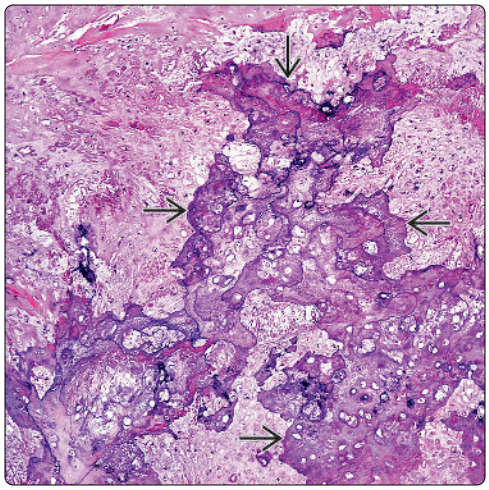


**(Left)** *A nodule of unmineralized hyaline cartilage in an enchondroma is framed by a rim of mineralized reactive bone. This type of configuration produces the histologic correlate of the "O" ring sign that is characteristic of enchondroma on radiographs. The marrow is replaced by fibrous tissue because of a nearby fracture.* **(Right)** *Peripheral edge of hypocellular enchondroma shows that it is rimmed by a layer of reactive bone. The adjacent marrow is unremarkable.*

### Periphery of Enchondroma

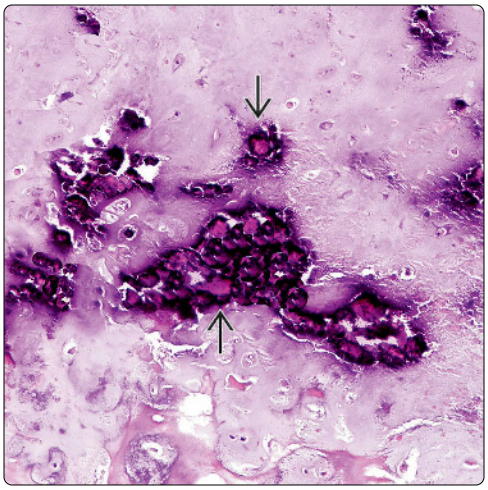


### Areas of Mineralization



**(Left)** *An area of an enchondroma contains an irregular region of calcification, which appears dark purple in color. The mineral is calcium hydroxyapatite and is deposited in a blotchy fashion. The chondrocytes undergo necrosis when the surrounding matrix calcifies.* **(Right)** *A specimen of an enchondroma that has not been decalcified prior to histologic sectioning is shown. The irregular, dense mineral stains a dark purple. The amount of calcification is very variable.*

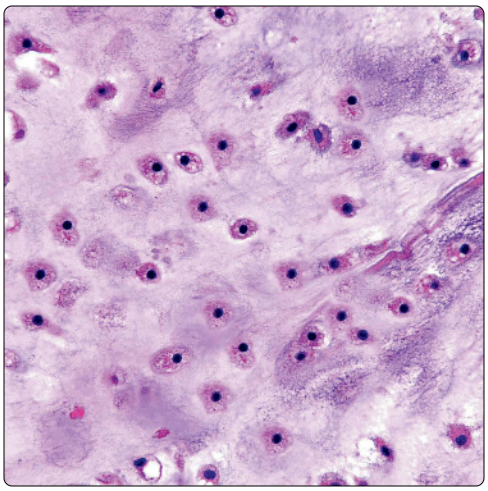
### Calcifications



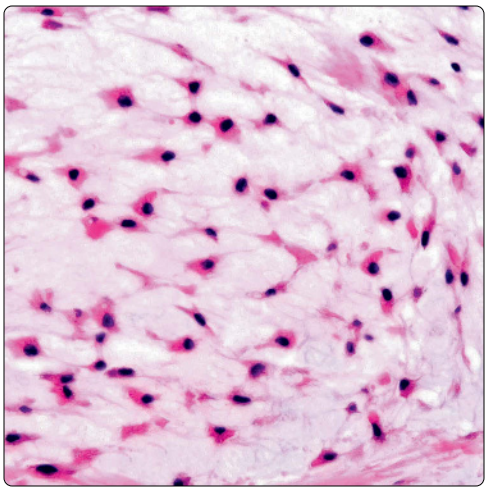


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### Cytologic Features

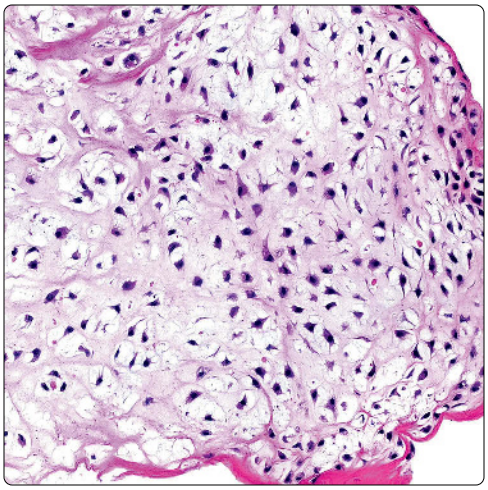


### Myxoid Change

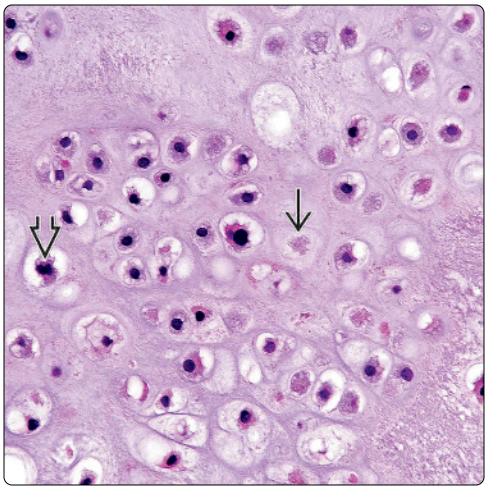


**(Left)** *An enchondroma is composed of well-formed hyaline cartilage. The tumor is moderately cellular, and the chondrocytes are randomly scattered throughout the matrix. The chondrocytes have small, round, dark-staining nuclei and lack nucleoli.* **(Right)** *An enchondroma contains a small focus of myxoid cartilage. The chondrocytes are spindle or stellate-shaped and float in the frothy basophilic extracellular matrix; there are no lacunar spaces. The chondrocyte nuclei are banal.*

### Increased Cellularity

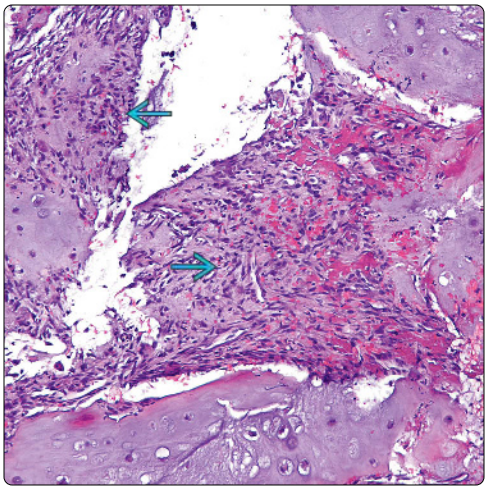


### Cellular Digital Enchondroma

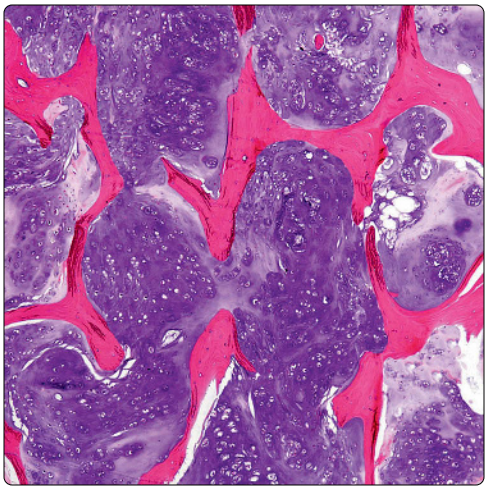


**(Left)** *Digital enchondroma shows the characteristic increase in cellularity for tumors originating in this anatomic location. The matrix is hyaline, and the neoplastic cells reside in lacunar spaces.* **(Right)** *Cellular digital enchondroma shows chondrocytes that demonstrate limited cytologic atypia. Features to note are variability in the size of the nuclei and the occasional binucleate cell. Scattered cells have undergone necrosis and lack nuclei.*

### Fractured Enchondroma



### Low-Grade Chondrosarcoma



**(Left)** *Curettage from an enchondroma that had undergone a pathologic fracture is shown. Adjacent to the cartilage nodules there is a reactive fibrovascular proliferation. This should not be mistaken for a dedifferentiation.* **(Right)** *Unlike enchondroma that is well demarcated and rimmed by reactive bone, low-grade chondrosarcoma demonstrates an infiltrative growth pattern, encasing preexisting trabecular bone, as seen in this case.*



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KEY FACTS

## TERMINOLOGY

- Multiple enchondromas that are associated with Ollier disease and Maffucci syndrome
- Maffucci syndrome defined as ≥ 2 enchondromas associated with extraosseous hemangiomas
- Ollier disease defined as ≥ 2 enchondromas

## CLINICAL ISSUES

- Frequently 1st noted during childhood
- Frequently affects short tubular bones of hands
- Hemangiomas of Maffucci syndrome usually located in skin or soft tissue
- May have anywhere from 2 to hundreds of tumors
- Painful lesions need to be biopsied and possibly removed
- Patients with Ollier disease or Maffucci syndrome must have lifetime monitoring of their tumors

## IMAGING

- Tumors are multiple
- Some lesions may arise within medullary cavity and resemble solitary enchondroma

## MACROSCOPIC

- Multiple nodules
- Gray, glistening in appearance

## MICROSCOPIC

- Frequently demonstrates increased cellularity and cytologic atypia compared to sporadic enchondromas but lacks infiltrative growth pattern
- May contain myxoid matrix

## TOP DIFFERENTIAL DIAGNOSES

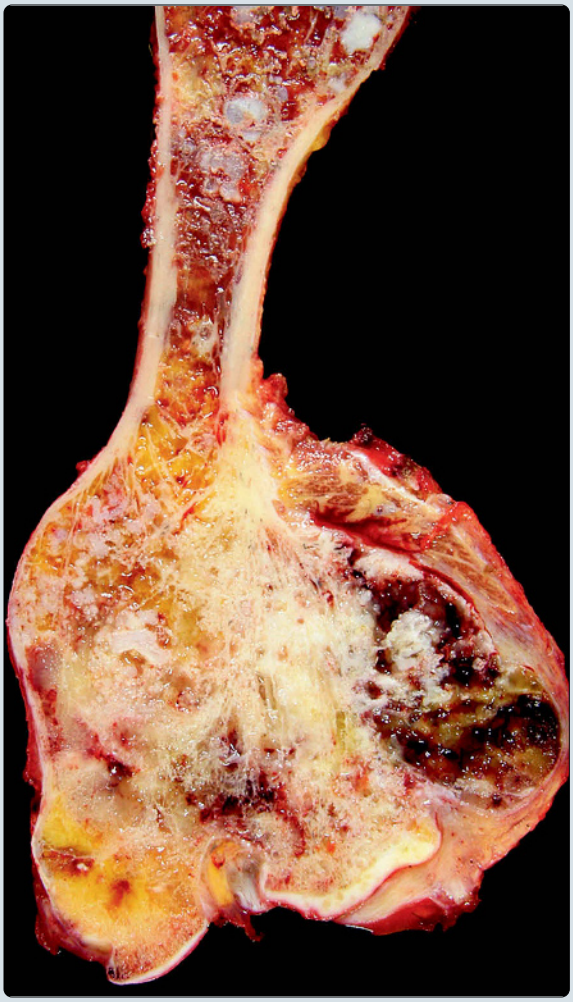
- Chondrosarcoma
- In small sample, can be very difficult to distinguish enchondromas in Ollier disease and Maffucci syndrome from low-grade chondrosarcoma
- Most important histologic feature is demonstration of infiltrative growth pattern in chondrosarcoma

**Chondrosarcoma Arising in Enchondromatosis**



*Radiograph of the right knee shows extensive deformity and shortening of the femur and tibia. The metaphyses of both bones are expanded and contain punctuate cartilaginous calcifications.*

**Chondrosarcoma Arising in Enchondromatosis**



*Transformation to chondrosarcoma is shown in longstanding enchondromatosis of the distal femur. Gray, glistening enchondromas and a destructive hemorrhagic chondrosarcoma are noted.*



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## TERMINOLOGY

### Definitions

- Multiple enchondromas may be associated with Ollier disease or Maffucci syndrome
  - 90% of patients with multiple enchondromas have Ollier disease; 10% are associated with Maffucci syndrome
- Ollier disease defined as ≥ 2 enchondromas usually affecting short and long tubular bones
- Maffucci syndrome defined as ≥ 2 enchondromas associated with extraosseous hemangiomas
  - Hemangiomas were originally classified as cavernous hemangiomas or arteriovenous malformations
    - More recent studies have shown that most of these vascular tumors are spindle cell hemangiomas

## ETIOLOGY/PATHOGENESIS

### Neoplastic

- Recently, enchondromas in Ollier disease and Maffucci syndrome have been shown to be caused by somatic mutation involving *IDH1* and *IDH2*

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Rare; exact incidence not known
- Age
  - Frequently noted during childhood
  - In patients with Ollier disease, cartilage tumors may stabilize in size after puberty or continue to grow
- Sex
  - Equal distribution

### Site

- Enchondromas may involve
  - Only small bones of hands and feet; only long bones, scapulae, and pelvis; small, long and flat bones
  - Involvement of vertebrae and skull is rare
- Tends to affect one side of body more severely than other
- Within long bones, enchondromas usually metaphyseal-diaphyseal in location
- Hemangiomas in patients with Maffucci syndrome are usually located in skin or soft tissue
  - May be centered in viscera
- One site of body frequently more severely affected

### Presentation

- Variable: Frequently, initial symptom is related to enlargement of fingers; patients may have anywhere from 2 to hundreds of tumors
- May be asymptomatic, especially if there are only few enchondromas; may cause severe mechanical and cosmetic problems

### Natural History

- In patients with Ollier disease, cartilage tumors may stabilize in size after puberty or continue to grow
- Development of malignancies within viscera as well as in enchondromas is an important aspect of Maffucci syndrome
  - Carcinomas of pancreas and malignancies of ovaries, brain, and skeleton commonplace in Maffucci syndrome
- Chondrosarcoma is major malignancy associated with Ollier disease

### Treatment

- No specific treatment; painful lesions may have to be removed; forms of corrective surgery, including amputation, may be necessary for severe deformities
- Treatment as needed for nonosseous lesions of Maffucci syndrome

### Prognosis

- Overall risk of malignant transformation into chondrosarcoma is 40%; more common in patients with severe skeletal involvement or involvement of long and flat bones

## IMAGING

### Radiographic Findings

- Tumors are multiple; some may arise within medullary cavity and resemble solitary enchondroma
- Others may be eccentric, arise in cortex or on surfaces of bone, and even span joints
- In long bones, persistent columns of dysplastic cartilage that originate in growth plate produce linear radiolucencies that extend from metaphysis into diaphysis
  - Pathognomonic for either Ollier disease or Maffucci syndrome
- Severely affected bones shortened and deformed
- Phleboliths in soft tissue hemangiomas may be present in patients with Maffucci syndrome
- Destruction of bone and disappearance of previously seen matrix calcifications point to malignant degeneration

### MR Findings

- Low signal intensity on T2WI and high signal intensity on T2WI

### CT Findings

- Enchondromas are well circumscribed and show variable degree of calcifications

### Bone Scan

- Mild uptake: Demonstrates multiple lesions

## MACROSCOPIC

### General Features

- Multiple gray, glistening nodules that may coalesce into large masses

## MICROSCOPIC

### Histologic Features

- Similar to those of sporadic solitary enchondromas; frequently demonstrate greater degree of cellularity and cytologic atypia and may contain myxoid matrix

## SELECTED REFERENCES

1. Amary MF et al: Ollier disease and Maffucci syndrome are caused by somatic mosaic mutations of IDH1 and IDH2. Nat Genet. 43(12):1262-5, 2011



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### Cartilaginous Tumors



**(Left)** *Radiograph of the left humerus shows numerous cartilaginous tumors involving the metaphysis and diaphysis and the cortical surfaces. Their cartilaginous nature is revealed by the presence of punctuate and arcuate calcifications.* **(Right)** *Radiograph of the humerus in a patient with enchondromatosis shows medullary enchondromas, periosteal chondromas, and some cortical chondromas. Valgus deformity of the humerus is a common feature, presumably due to growth disturbance.*

### Valgus Deformity



### Medullary Enchondromas

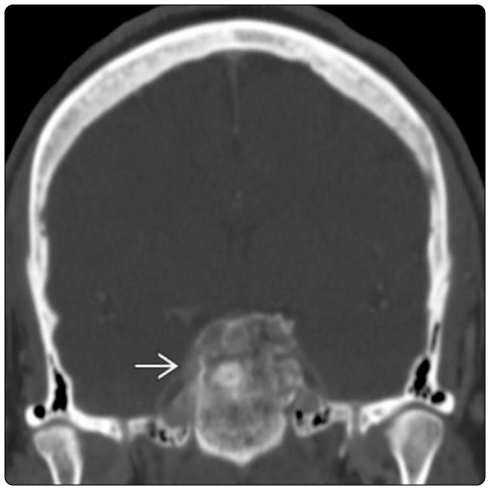


**(Left)** *Radiograph of the left humerus in a patient with enchondromatosis shows medullary enchondromas. Valgus deformity of the humerus is present.* **(Right)** *Radiograph of the hand shows cartilaginous tumors of the 2nd metacarpal and the 5th proximal phalanx. The lesion of the proximal phalanx is similar to a solitary enchondroma. The lesion of the 2nd metacarpal extends through the cortex to the periosteal surface at an oblique angle, presumably through a nutrient foramen, typical of enchondromatosis.*

### Enchondromatosis of Small Bones



### Skull Base Cartilaginous Tumor



**(Left)** *Coronal reformation of a CT scan from a patient with enchondromatosis shows a large, cartilaginous tumor of the skull base. The tumor is well demarcated and shows the typical arcs and rings of cartilaginous differentiation.* **(Right)** *Lateral radiograph of the humerus in a patient with enchondromatosis demonstrates a medullary expansile lytic lesion of the distal humerus. Although the tumor is entirely consistent with cartilage, there are no diagnostic features of enchondromatosis.*

### Expansile Lytic Lesion



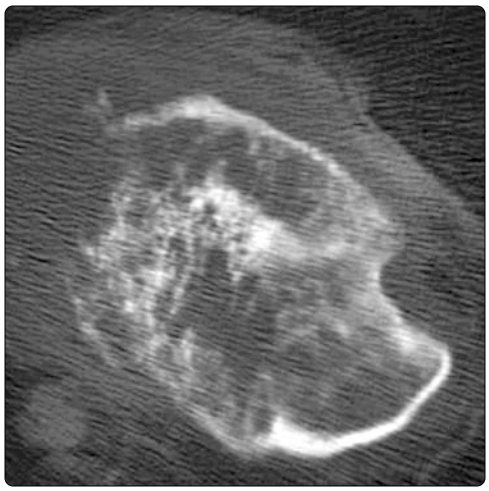


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### Cartilaginous Lesion

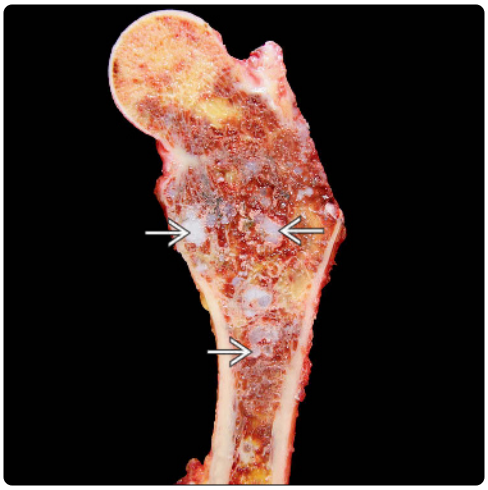


### Malignant Transformation



**(Left)** *CT scan of the ankle in a patient with enchondromatosis demonstrates a cartilaginous lesion of the distal fibula as well as the navicular. There are very large areas of the lesion that are not mineralized, suggesting recent growth and possibly malignant transformation.* **(Right)** *CT scan of the distal fibula in a patient with enchondromatosis shows a large cartilaginous lesion. In some areas, mineralized tissue is absent, indicating a chondrosarcomatous transformation.*

### Multiple Enchondromas



### Development of Chondrosarcoma



**(Left)** *Resection specimen of the proximal femur in a patient with enchondromatosis shows multiple well-circumscribed, gray, glistening nodules throughout the medullary cavity* ➔. **(Right)** *Chondrosarcoma arising in the proximal tibia in a patient with enchondromatosis is shown. The tumor arises in the medullary cavity, is gray and glistening as typically seen in chondrosarcoma, and has permeated the cortex and extended into the surrounding soft tissues* ➔.

### Deformity of Small Bones



### Chondrosarcoma of Finger

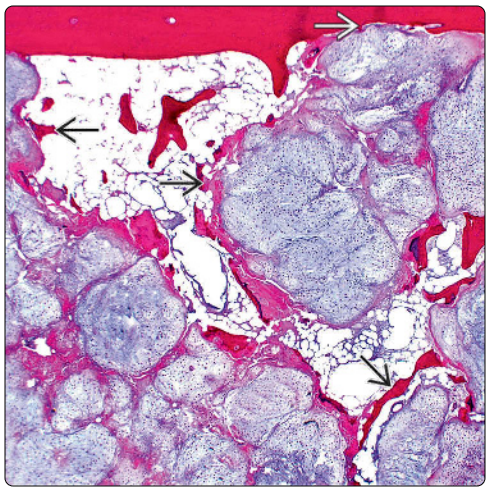


**(Left)** *Clinical photograph of a patient with enchondromatosis shows marked deformity of the fingers due to numerous intramedullary and parosteal chondromas.* **(Right)** *Finger resection specimen from a patient with low-grade chondrosarcoma associated with enchondromatosis shows many well-circumscribed, gray, glistening enchondromatous nodules* ➔, *especially in the proximal phalanx, that distally and proximally coalesce into a low-grade chondrosarcoma* ➔.

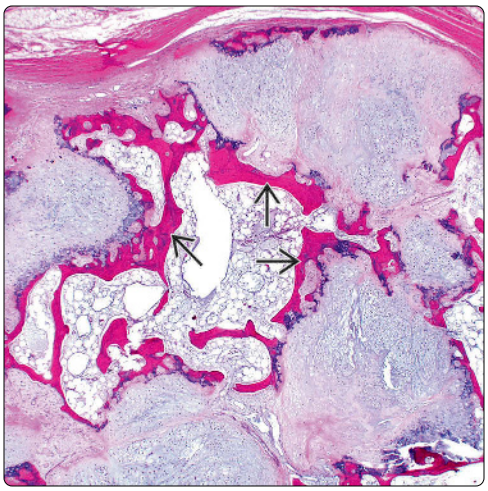


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### Multiple Enchondromas

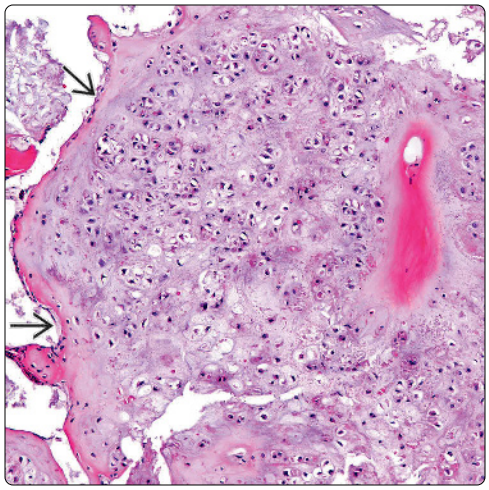


### Enchondromas Rimmed by Reactive Bone

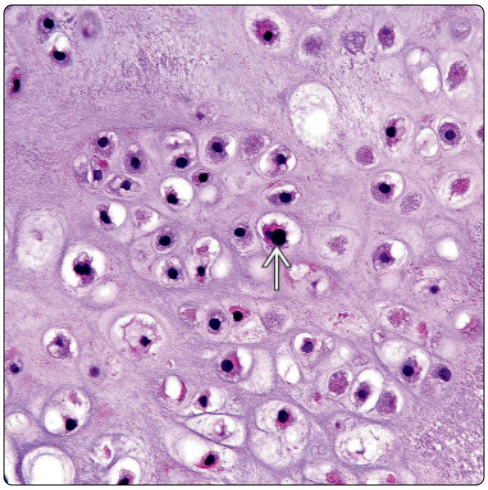


**(Left)** *Resection specimen from a patient with enchondromatosis shows multiple cartilaginous enchondromas. The individual nodules are well circumscribed, surrounded by reactive bone, and do not demonstrate an infiltrative growth pattern. There is focal scalloping of the cortex.* **(Right)** *Medium-power view shows the typical microscopic appearance of enchondromatosis. There are multiple cartilaginous nodules, which are rimmed by reactive bone and lack an infiltrative growth pattern.*

### Cellular Enchondroma

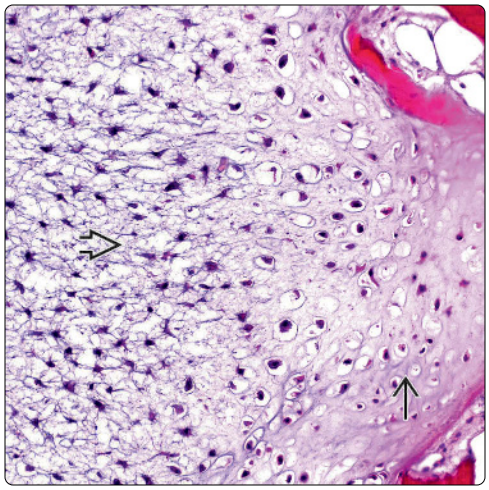


### Enchondroma With Cytologic Atypia

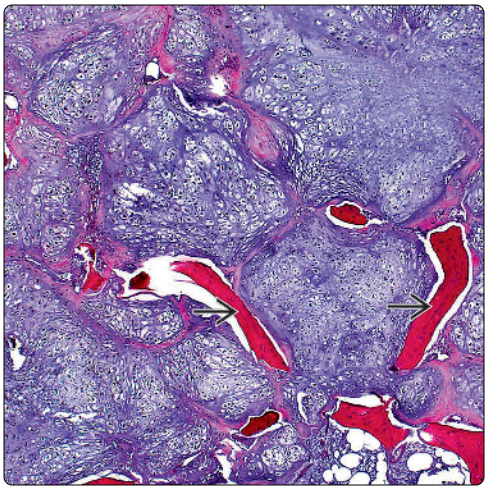


**(Left)** *High-power view of an enchondroma in a patient with enchondromatosis shows that the enchondromas frequently demonstrate increased cellularity and atypia, but the nodule is surrounded by a thin rim of reactive bone. Without an infiltrative growth pattern, these are not signs of malignancy.* **(Right)** *Higher power view shows increased cellularity and atypia. Some of the chondrocytes have enlarged hyperchromatic nuclei. This is a frequent finding in patients with enchondromatosis.*

### Enchondroma With Myxoid Change



### Infiltrative Growth Pattern

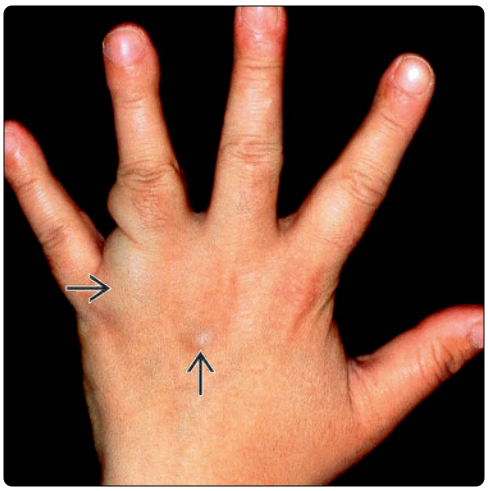


**(Left)** *In addition to increased cellularity and atypia, enchondromas in patients with enchondromatosis can show myxoid change, as in this tumor. The neoplastic cells are spindle- or stellate-shaped and do not reside in lacunae. Focal hyaline-type cartilage is present.* **(Right)** *Low-grade chondrosarcoma arising in a patient with enchondromatosis demonstrates the typical infiltrative growth pattern with the tumor replacing marrow spaces and encasing preexisting trabeculae of bone.*

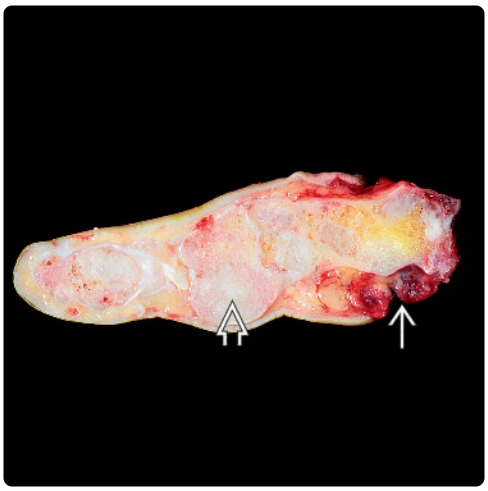


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### Spindle Cell Hemangiomas

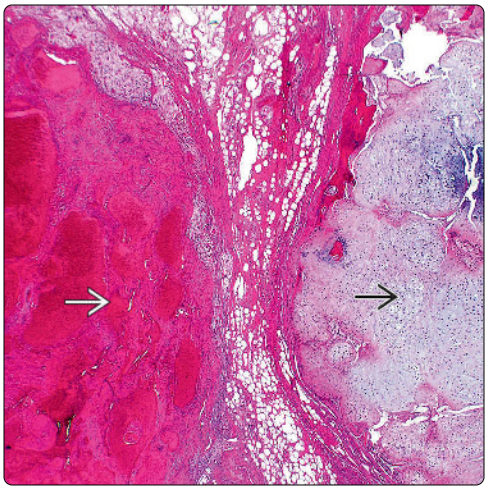


### Maffucci Syndrome

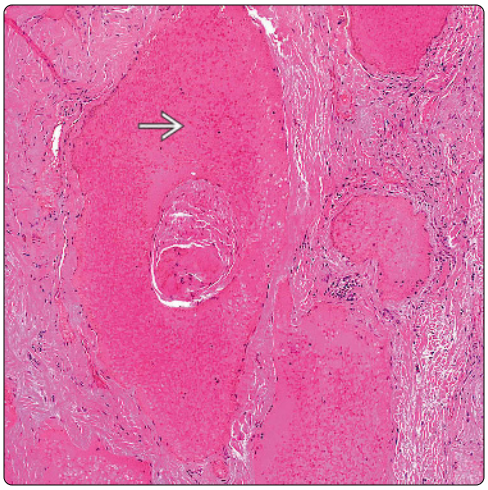


**(Left)** *Clinical photograph of a patient with Maffucci syndrome shows soft tissue spindle cell hemangiomas that have a vague bluish hue ⇨, the most common type of hemangioma arising in a patient with Maffucci syndrome.* **(Right)** *In this specimen from a patient with Maffucci syndrome, the bone is replaced by gray, glistening cartilaginous tumors, some of which are low-grade chondrosarcomas ➡. A small hemangioma ➡ is also present, confirming the diagnosis of Maffucci syndrome.*

### Enchondroma and Hemangioma

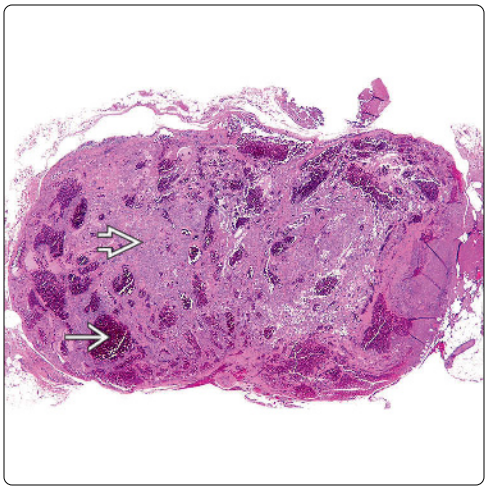


### Cavernous Hemangioma

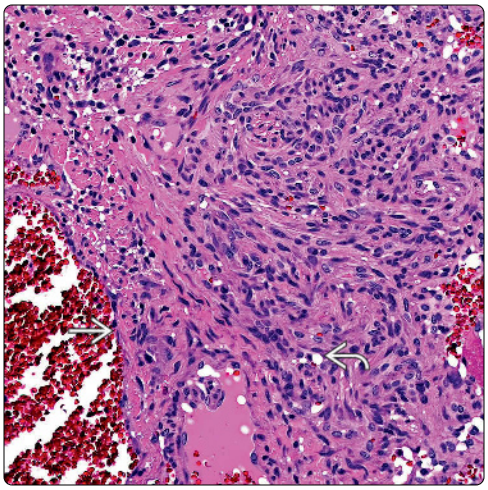


**(Left)** *Microscopic image from a patient with Maffucci syndrome shows a cellular enchondroma ⇨ adjacent to a soft tissue hemangioma ➡. This combination of enchondromatosis and hemangioma is diagnostic for Maffucci syndrome.* **(Right)** *Although most hemangiomas arising in patients with Maffucci syndrome are spindle cell hemangiomas, occasionally they are of the cavernous type, as seen here, composed of dilated vascular spaces ➡ lined by flat endothelial cells.*

### Spindle Cell Hemangioma



### Mimicking Kaposi Sarcoma



**(Left)** *Low-power view shows a spindle cell hemangioma in a patient with Maffucci syndrome. The tumor is well circumscribed and contains cavernous vascular spaces ➡ separated by more cellular areas ➡.* **(Right)** *Higher power view of spindle cell hemangioma in a patient with Maffucci syndrome shows a cavernous space lined by flattened endothelial cells ➡ and adjacent cellular spindled areas (Kaposi sarcoma-like). Some of the cells contain intracytoplasmic vacuoles ➡.*



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# Periosteal Chondroma

KEY FACTS

## TERMINOLOGY

- Relatively uncommon benign cartilage tumor that arises on cortex beneath periosteum
- Synonyms: Juxtacortical chondroma, subperiosteal chondroma

## CLINICAL ISSUES

- Males affected more frequently than females
- Develops in all age groups
- Treatment is excision of mass and overlying periosteum
- Recurrences are uncommon
- Mass and swelling
- Pain
- Surface of tubular bones are characteristic sites of origin

## IMAGING

- Predominately radiolucent
- May contain punctuate calcifications
- Has well-defined margins
- Periphery of tumor is delineated by thick, mature buttress of reactive periosteal bone
- Lesion is round or oval

## MACROSCOPIC

- Glistening, gray-white cartilage
- Focally gritty or mucinous

## MICROSCOPIC

- Neoplastic matrix is hypo- to moderately cellular
- Matrix is composed of hyaline cartilage
- Chondrocytes are usually bland
- No infiltration into underlying bone present

## TOP DIFFERENTIAL DIAGNOSES

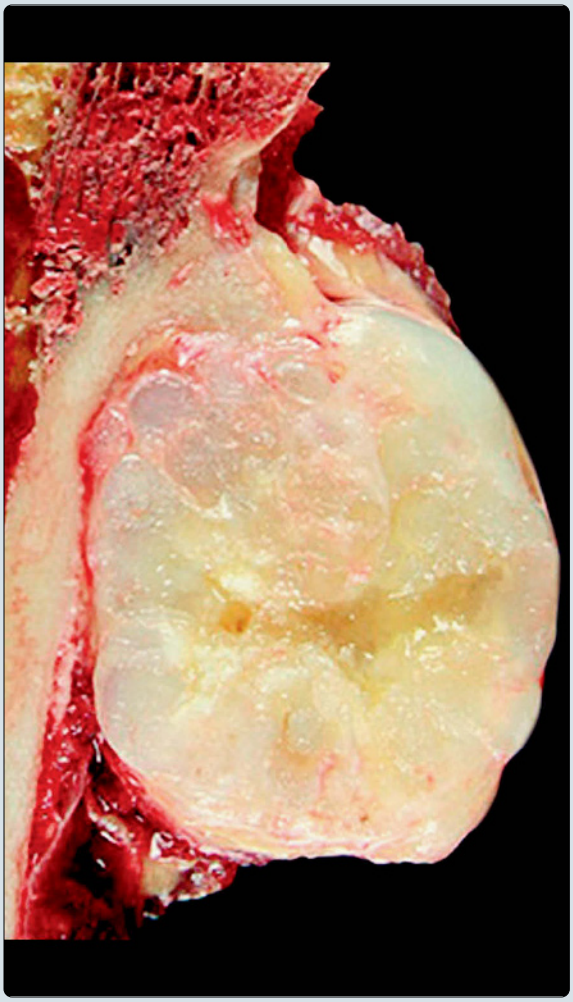
- Periosteal chondrosarcoma and osteosarcoma
- Bizarre parosteal osteochondromatous proliferation
- Periosteal chondromyxoid fibroma
- Parosteal osteosarcoma

**Multinodular Surface Chondroma**



*Large periosteal chondroma of the proximal humerus presenting as a multinodular mass is delineated peripherally by a rim of reactive bone imparting a trabeculated appearance to the tumor.*

**Lobulated Glistening Tumor**



*Periosteal chondroma is composed of lobules of well-formed hyaline cartilage that coalesce into a solitary mass. The tumor is partially demarcated by a thin rim of well-formed reactive bone.*



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## TERMINOLOGY

### Synonyms

- Juxtacortical chondroma; subperiosteal chondroma

### Definitions

- Relatively uncommon benign cartilage tumor that arises on surface of cortex beneath periosteum

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - < 1% of all chondromas
- Age
  - Develops in all age groups; can occur in children and older adults; most patients in 2nd or 3rd decade of life
- Sex
  - Males affected more frequently than females

### Site

- Surfaces of tubular bones are characteristic sites of origin
  - Particularly metaphyseal or diaphyseal regions of humerus and femur and short tubular bones of hand and foot
- May also arise on surface of vertebrae

### Presentation

- Mass, swelling, pain; may be caused by involvement of tendinous insertion site by tumor
- May cause spinal cord compression and neurologic symptoms when involving vertebrae

### Treatment

- Excision of cartilaginous mass, including overlying periosteum

### Prognosis

- Recurrences are uncommon; malignant transformation is extremely rare

## IMAGING

### Radiographic Findings

- Predominately radiolucent, surface lesion; may contain punctuate calcifications
- Has well-defined margins
- Underlying cortex is superficially eroded; occasionally scalloped and sclerotic but not transgressed
- Periphery of tumor is delineated by thick, mature buttress of reactive periosteal bone; results in appearance that has been likened to egg in cup

### MR Findings

- Similar to other benign cartilage tumors; bright on T2- and dark on T1-weighted images
- Underlying medullary cavity may show marrow edema mimicking marrow involvement by tumor
- May show peripheral enhancement

### CT Findings

- Shows size and round or oval shape
  - Clearly identifies extent of tumor and lack of involvement of medullary cavity
  - May show matrix calcifications and scalloping of underlying cortex

## MACROSCOPIC

### General Features

- Glistening, gray-white cartilage; focally gritty or mucinous
- Periosteum, layer of firm fibrous connective tissue, covers tumor
- Base is smooth or undulating and sharply demarcated from underlying excavated cortex
- Medullary cavity may be impinged upon by reactive endosteal bone but is uninvolved

### Size

- Rarely exceeds 3 cm in size; if larger, possibility of periosteal chondrosarcoma should be considered

## MICROSCOPIC

### Histologic Features

- Neoplastic matrix is hypo- to moderately cellular; chondrocytes are bland
- May demonstrate mild to moderate atypia in form of nuclear enlargement, prominent nucleoli, and binucleation
- Matrix is composed of hyaline cartilage; may be focally myxoid

## DIFFERENTIAL DIAGNOSIS

### Periosteal Chondrosarcoma

- Can be difficult to distinguish from periosteal chondroma
- Usually larger, more cellular, and demonstrate more cytologic atypia than periosteal chondromas

### Periosteal Osteosarcoma

- Demonstrates more cytologic atypia and contains neoplastic bone formation

### Bizarre Parosteal Osteochondromatous Proliferation

- Composed of reactive fibrous tissue with cellular cartilaginous cap, which undergoes endochondral ossification

### Periosteal Chondromyxoid Fibroma

- Has lobulated growth pattern; myxoid areas are prominent as well as chondroid areas
- Nonchondroid areas contain spindle- or stellate-shaped cells within myxoid or fibromyxoid stroma

### Parosteal Osteosarcoma

- May contain cartilaginous cap
  - Cartilaginous cap is disorganized and may demonstrate endochondral ossification
- Additionally contains malignant spindle-shaped cells and neoplastic bone

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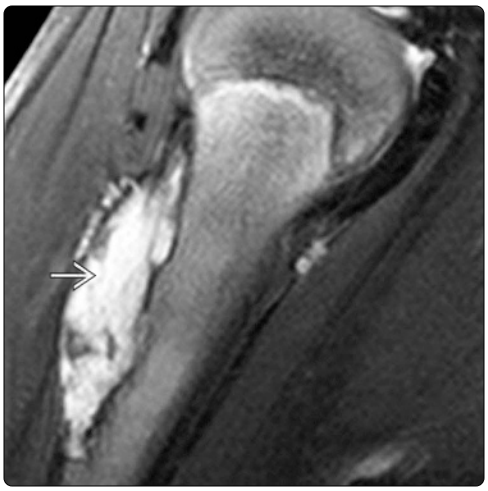


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**Radiolucent Lesion**



**Bright on T2-Weighted MR**



**(Left)** *AP radiograph of the elbow demonstrates a radiolucent lesion arising on the surface of the humerus. The lesion is spherical, contains very faint internal mineral deposits, and is bound peripherally by a rim of subperiosteal reactive bone.* **(Right)** *Sagittal T2 FS MR shows an elongated lesion on the surface of the humerus, resulting in slight excavation of the cortex but no marrow invasion. The lesion is very bright on T2 images, typical of cartilage.*

**Surrounding Reactive Bone**



**T2-Bright Surface Tumor**



**(Left)** *Coronal reformation of CT scan shows a lesion arising on the surface of the proximal humerus. The tumor is partially surrounded by a thick buttress of reactive bone and is radiolucent (darker than muscle), consistent with the high water content of cartilage.* **(Right)** *Surface chondroma of the phalanx is shown. The tumor is lobulated, well demarcated, and bright on this T2-weighted image. It has focally extended through the cortex to involve the underlying medullary cavity.*

**Faintly Mineralized Tumor**



**Surface Chondroma**

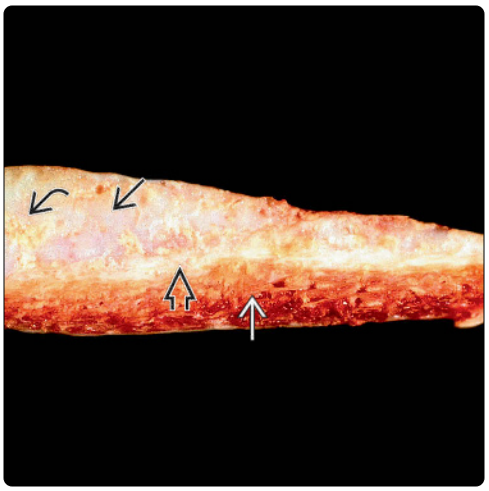


**(Left)** *Lateral radiograph of the knee shows a periosteal chondroma on the posterior femoral surface. The lesion contains faint internal mineral deposits.* **(Right)** *Sagittal fat-suppressed T1-weighted MR after intravenous contrast shows the surface lesion composed of multiple nodules of cartilage. A tiny focus of dark signal within each nodule probably represents calcification. There is little enhancement, typical of the hypovascular nature of cartilage.*

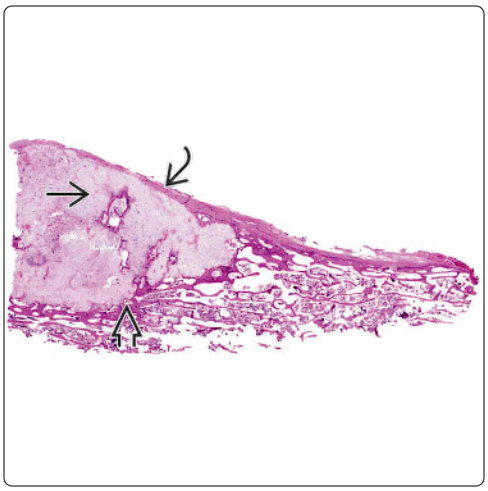


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### Nodules of Hyaline-Type Cartilage

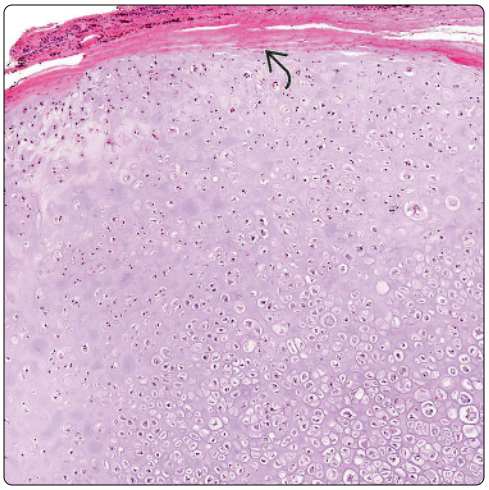


### Subperiosteal Tumor

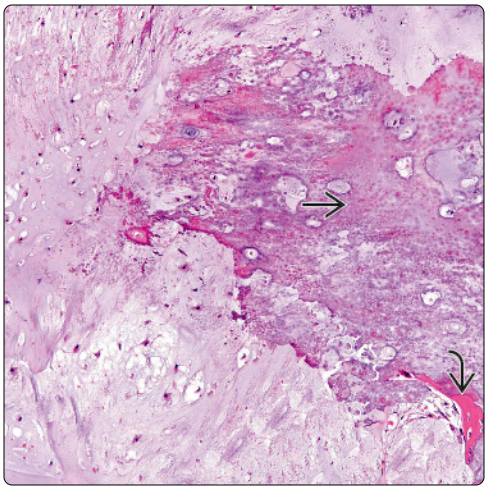


**(Left)** *Periosteal chondroma of the humerus is composed of nodules of blue-gray hyaline cartilage that show peripheral enchondral ossification. The tumor is firmly anchored to and sharply demarcated from the underlying cortex. The medulla is not involved by the tumor.* **(Right)** *Whole-mount section shows periosteal chondroma composed of lobules of hyaline cartilage. The periphery of the tumor is covered by the periosteum, and the cortex is scalloped.*

### Cellular Tumor

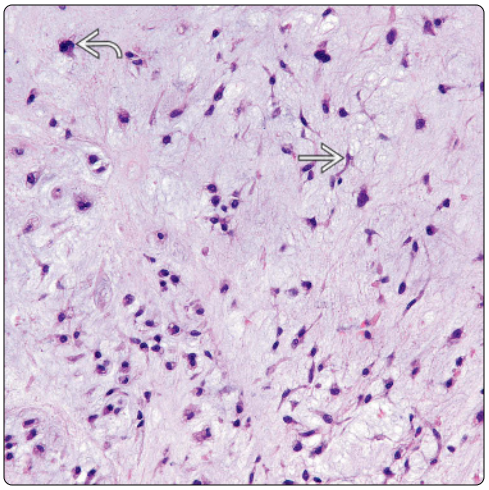


### Calcified Surface Chondroma

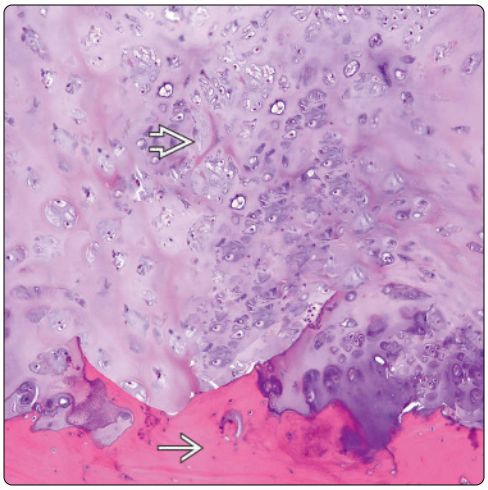


**(Left)** *The overlying periosteum is composed of a thin layer of dense fibrous tissue. The tumor consists of nodules of moderately cellular hyaline cartilage with the neoplastic chondrocytes residing in lacunar spaces.* **(Right)** *The neoplastic cartilage of periosteal chondroma is predominately hyaline and may contain areas that are calcified. The calcification appears as amorphous purple granularity. Foci of enchondral ossification may also be present.*

### Hypercellular Lesion With Cytologic Atypia



### Sharp Margin With Cortex



**(Left)** *Hypercellularity, cytologic atypia (nuclear enlargement and hyperchromasia), and focal myxoid change may also be present in periosteal chondroma, making it challenging to distinguish from periosteal chondrosarcoma. In the myxoid areas, the chondrocytes are stellate and do not reside in lacunar spaces.* **(Right)** *The base of the periosteal chondroma is usually attached directly to the underlying cortex. The margin is sharp and often undulating.*



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# Chondroblastoma

KEY FACTS

## CLINICAL ISSUES

- Age range: 10-25 years
- Skeletally immature individuals
- Usually treated by curettage; recurrence rate 14-18%
- Pulmonary metastases from histologically benign chondroblastomas uncommon

## IMAGING

- Intramedullary, well-defined tumor with sclerotic margins
- Radiolucent with internal calcifications

## MACROSCOPIC

- Gritty
- Grayish-white
- Hemorrhagic cystic areas common

## MICROSCOPIC

- Densely cellular
- Composed of admixture of mononuclear chondroblasts and multinucleated osteoclast-type giant cells
- Chondroblasts grow in sheets
- Matrix generally consists of poorly formed hyaline cartilage

## ANCILLARY TESTS

- Chondroblasts express S100 protein and SOX9
- Mutation in chromatin protein histone H3.3 present in most chondroblastomas

## TOP DIFFERENTIAL DIAGNOSES

- Chondromyxoid fibroma
- Aneurysmal bone cyst
- Clear cell chondrosarcoma
- Giant cell tumor of bone
- Chondroblastoma-like osteosarcoma

## DIAGNOSTIC CHECKLIST

- Think chondroblastoma if you see tumor located in epiphysis in skeletally immature individual

**Lytic Tumor in Femoral Head**

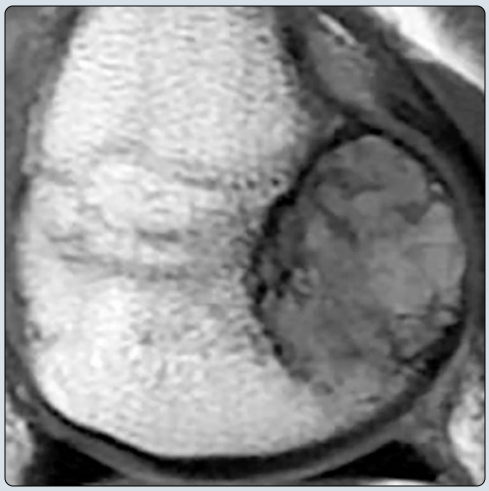


**Lytic Tumor Occupying Femoral Head**

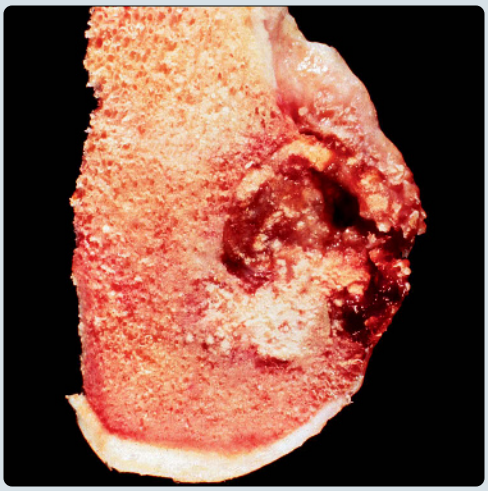


**(Left)** *The chondroblastoma manifests as an oval, well-circumscribed, lytic mass in the femoral head. A few small, punctate areas of mineralization are present.* **(Right)** *Coronal CT scan shows a homogenous mass filling much of the femoral head. The tumor has the density of soft tissue and, in this example, is homogenous. In areas, the margins of the tumor are sclerotic.*

**Tumor in Femoral Condyle**



**Red-Tan-White, Well-Circumscribed Mass**



**(Left)** *Sagittal T1-weighted MR shows a lobulated, heterogeneous, low-intensity mass present beneath the articular surface of the posterior femoral condyle. The tumor is well circumscribed, and there is mild peritumoral edema.* **(Right)** *Chondroblastoma grossly manifests as a round to oval, soft to gritty, red-tan-white mass. The margins are well circumscribed. In this case, the tumor is located beneath the articular cartilage.*



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## TERMINOLOGY

### Synonyms

- Calcifying giant cell tumor
- Codman tumor
- Epiphyseal chondromatous giant cell tumor

### Definitions

- Benign, cartilage-producing neoplasm composed of chondroblasts that arises in epiphysis of skeletally immature individuals

## ETIOLOGY/PATHOGENESIS

### Genetic Aberration

- Presumably develops from mutations in intraosseous mesenchymal stem cells

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Accounts for ~ 1% of primary bone tumors
  - Responsible for < 3% of primary benign bone tumors
  - In individuals younger than 18 years, incidence is 1.18 per million
- Age
  - 10-25 years with open growth plates
  - Rare in young children and elderly
- Sex
  - More common in males
    - M:F = 2:1

### Site

- Bones that form via endochondral ossification
- Epiphysis of long tubular bones: 66%
  - Distal and proximal femur, proximal tibia, and proximal humerus
  - ~ 37% limited to epiphysis
  - ~ 65% involve epiphysis and extend into metaphysis
  - Vast majority are centered in medullary cavity; intracortical and surface tumors are rare
- Apophyseal origin is less frequent: 25%
  - Greater trochanter of femur; greater tuberosity of humerus
- Bones of hands and feet: 10%
- Other locations include talus, calcaneus, patella, acetabulum, iliac crest, temporal bone, and skull base
- Tumors arising in metaphysis or diaphysis rare
- Almost all chondroblastomas are solitary
  - Multifocal chondroblastoma is very rare
- Adults have tumors in unusual locations: Craniofacial bones

### Presentation

- Pain, swelling, stiffness
- Limitation of range motion
- Limp
- Pathologic fracture through articular surface

### Natural History

- Slow enlargement, progressive symptoms
- May locally recur following curettage or incomplete resection
- Metastases develop in < 1% of patients
  - Usually follows multiple recurrences or pathologic fracture
- Malignant transformation very rare

### Treatment

- Curettage and packing with bone graft
- Percutaneous radiofrequency heat ablation
- Resection in selected cases
- Radiation of tumors that are in critical anatomic locations: Skull base

### Prognosis

- Local recurrence rate: 14-18%
- Higher recurrence rate in tumors arising in temporal bone and ribs
- Local recurrences usually develop within 3 years following curettage
  - May be detected after much longer time interval
- Pulmonary metastases from histologically benign chondroblastomas
  - Metastases are slowly progressive
  - Maintain histology of benign chondroblastoma
  - Usually develop > 5 years after primary diagnosis
  - Rarely fatal and can be treated with resection

## IMAGING

### Radiographic Findings

- Intramedullary, eccentric or central, well-defined sclerotic margins
- Predominately radiolucent often contains scattered punctate calcifications
- May scallop cortex or result in its destruction
- Neighboring marrow edema
- Secondary aneurysmal bone cyst-like changes may cause extensive expansion of bone and periosteal reaction mimicking more aggressive neoplasm
  - May be difficult to identify features of underlying primary chondroblastoma

### MR Findings

- Low or intermediate signal intensity on T1-weighted image and may be obscured by surrounding edema
- High or variable intensity on T2-weighted image
- Prominent edema in marrow and soft tissue
- Joint effusion is common

### CT Findings

- Oval, well demarcated with internal calcifications

### Bone Scan

- Marked avidity on bone scan

## MACROSCOPIC

### General Features

- Well circumscribed, round or oval, red-gray-white, and gritty
- Hemorrhagic cystic areas common and may be prominent mimicking aneurysmal bone cyst



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### Size

- Range in size from 1-19 cm (average: 3.6 cm)
- 85% are ≤ 5 cm

## MICROSCOPIC

### Histologic Features

- Hypercellular with sharp margins
- Admixture of mononuclear chondroblasts and multinucleated osteoclast-type giant cells
- Chondroblasts grow in sheets and have eosinophilic cytoplasm with well-defined cell membranes and eccentric nuclei
- Nuclei are reniform or coffee bean-shaped; similar in appearance to nuclei of Langerhans cells
- Mitotic activity and regional necrosis may be present; latter common in calcified areas
- Chondroid matrix can be pink or basophilic and sometimes resemble woven bone
  - Well-formed hyaline cartilage uncommon
- Mineralization of matrix surrounding single cells imparts chicken-wire pattern
- Osteoclast-type giant cells scattered throughout tumor; numerous in areas of matrix production and hemorrhage
  - Osteoclast-type giant cells are nonneoplastic
- Chondroblastoma of temporomandibular joint have intracytoplasmic hemosiderin deposition mimicking tenosynovial giant cell tumor
  - Some cases reported in literature likely represent tenosynovial giant cell tumor
- Vascular invasion uncommon
- Term aggressive chondroblastoma is used for tumors that histologically have features of chondroblastoma but show destructive growth pattern radiographically
- Tumor in metastatic deposits similar to that of primary and frequently surrounded by rim of reactive bone

## ANCILLARY TESTS

### Immunohistochemistry

- Chondroblasts express S100 protein and SOX9
  - Sometimes S100 is negative or very focal
- May stain with muscle actin, keratin, and epithelial membrane antigen
- RANKL, stimulator of osteoclast production and activity, is expressed by tumor cells
  - Recruits osteoclasts into tumor
- Extracellular matrix stains for collagen type II
- Stain for H3F3 K36M protein recently created are relatively specific for chondroblastoma

### Genetic Testing

- Mutation in chromatin histone gene, *H3F3A* (H3F3A), present in most chondroblastomas
  - Results in change from lysine to methionine in protein
- Clonal abnormalities especially involving chromosomes 5 and 8 have been identified
  - Some tumors have balanced t(5;17)

## DIFFERENTIAL DIAGNOSIS

### Chondromyxoid Fibroma

- Usually arises in metaphysis and not epiphyses
- Lobulated contour with chondromyxoid areas
- No chicken-wire pattern of mineralization

### Aneurysmal Bone Cyst

- Lacks chondroblasts and neoplastic cartilaginous matrix
- Cyst wall composed of spindle cells, osteoclast-type giant cells, and reactive woven bone

### Clear Cell Chondrosarcoma

- Arises in epiphyses in skeletally mature patients with closed growth plates
- Infiltrative growth pattern and contains areas of conventional chondrosarcoma and cells with abundant clear (glycogen-filled) cytoplasm

### Giant Cell Tumor of Bone

- Large tumor that spans epiphysis and metaphysis
- Arises in adults
- Nuclei of mononuclear cells are morphologically identical to nuclei of osteoclast-type giant cells
- Mononuclear cells are S100 negative
- Does not contain chondroid matrix or calcifications
- Frequently has areas where tumor cells are spindle-shaped

### Chondroblastoma-Like Osteosarcoma

- Tumor cells are similar to mononuclear cells in chondroblastoma and can express S100 protein
- Tumor grows with infiltrative growth pattern
- Tumor cells demonstrate greater degree of cytologic atypia
- Osteosarcoma is more aggressive radiographically

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Think chondroblastoma if you see tumor located in epiphysis in skeletally immature individual

### Pathologic Interpretation Pearls

- Cellular tumor in which mononuclear cells have eccentric cleaved nuclei mimicking nuclei seen in Langerhans cell histiocytosis
  - With chicken-wire pattern of mineralization and scattered osteoclast-like giant cells

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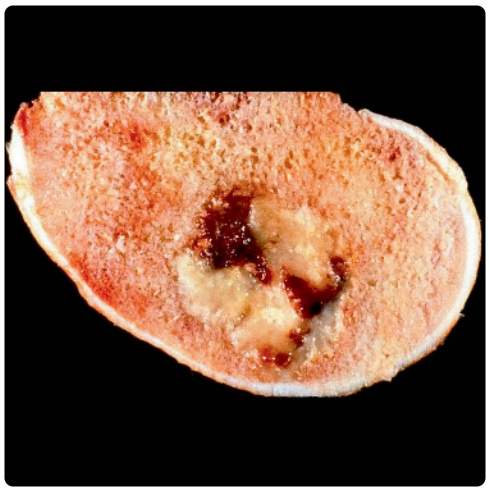



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### Mixed Lytic and Calcified Mass

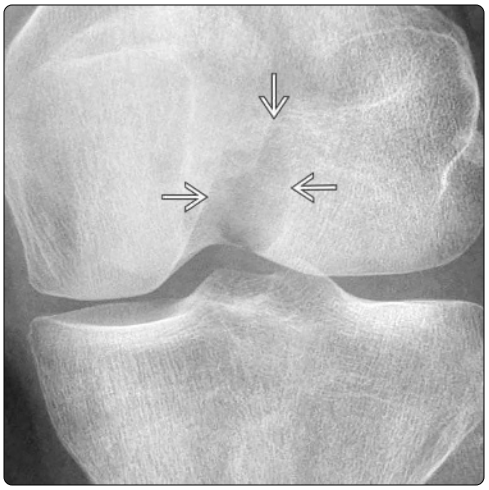


### Oval, Red-Tan Mass

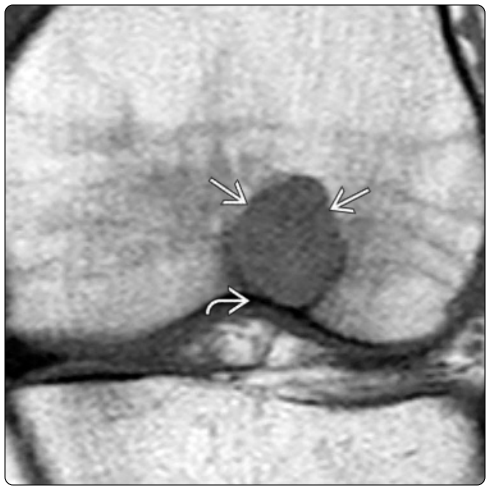


**(Left)** *Specimen radiograph shows chondroblastoma of the femoral condyle. The large tumor fills the medullary cavity, has a lobular configuration, a sharp sclerotic margin, and is lucent with internal mineralization.* **(Right)** *Resected femoral condyle contains an intramedullary chondroblastoma. The oval tumor is well circumscribed and red-tan in appearance. The overlying articular cartilage is unremarkable.*

### Lytic Tumor in Intercondylar Notch



### Low-Density Mass



**(Left)** *This chondroblastoma is located in the intercondylar notch of the distal femur ➔. The tumor is lytic and has well-circumscribed margins.* **(Right)** *Coronal T1-weighted MR shows an oval, small, low-density mass ➔ in the intercondylar notch. The tumor has well-circumscribed margins and is adjacent to the subchondral bone plate ➔.*

### Oval and Lytic Tumor in Talus



### Subchondral Multinodular Tumor

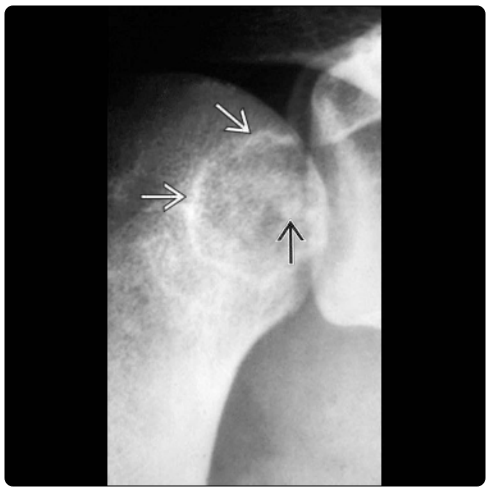


**(Left)** *Within the dome of the talus is a lytic, oval, well-circumscribed tumor ➔. The margins of the mass are sclerotic.* **(Right)** *Corresponding coronal MR shows that the chondroblastoma ➔ has a nodular architecture and well-circumscribed margins that are sclerotic. The tumor extends to the base of the articular surface ➔.*

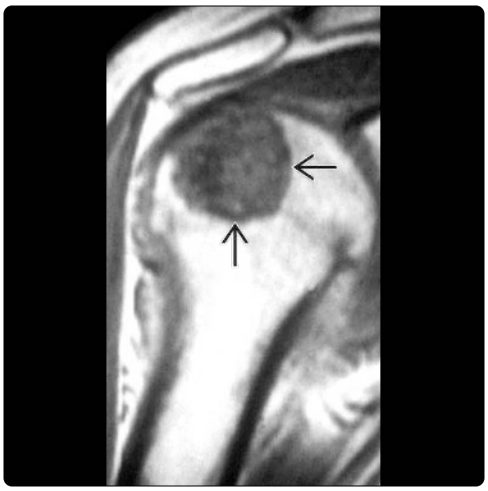


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### Chondroblastoma of Humeral Head



### Tumor Centered in Epiphysis

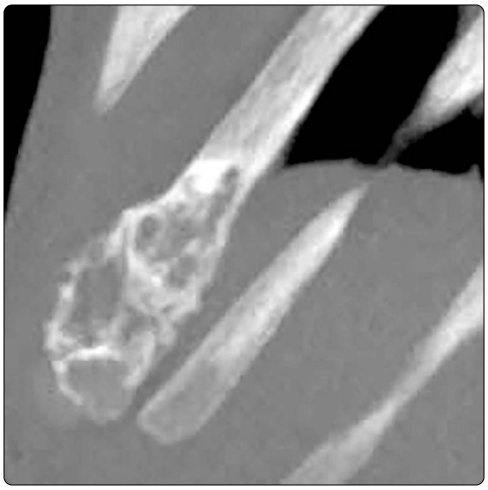


**(Left)** *Internally rotated view of the shoulder shows a chondroblastoma in the humeral head. Within the lesion are scattered, cartilaginous matrix densities. There is reactive sclerosis surrounding the lesion. The humeral head is subluxed inferomedially by a joint effusion.* **(Right)** *Coronal T1-weighted MR shows a well-demarcated lesion in the superolateral humeral head with heterogeneous internal signal. The surrounding marrow is normal. The growth plate is fused.*

### Expansile Mass of Rib



### Irregular Expansile Mass



**(Left)** *In this 3D reformatted CT, the chondroblastoma manifests as an expansile mass at the anterior end of the rib adjacent to the costal cartilage. The web-like bone is reactive and surrounds the periphery of the tumor.* **(Right)** *This chondroblastoma of the rib has arisen at the end of the rib in close proximity to the costal cartilage. The multinodular tumor is lytic, expansile, and, in areas, has eroded the cortex.*

### Lytic and Mineralized Mass in Condyle



### Tumor Distorts Mandibular Condyle



**(Left)** *The condyle of the mandible is expanded by a lytic tumor that contains focal areas of mineralization. The tumor has destroyed the cortex and is surrounded by a thin layer of reactive bone.* **(Right)** *In this accompanying 3D reformatted CT scan, the chondroblastoma expands the mandibular condyle.*



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### Destructive Mass in Calcaneus



### Hemorrhagic Mass in Talus



**(Left)** *A large chondroblastoma has destroyed a large portion of the talus. The tumor extends to the base of the proximal articular surface to the articulation with calcaneus. The intramedullary margin* ➔ *is well circumscribed, and the posterior component is surrounded by reactive bone* ➔. **(Right)** *The focally hemorrhagic chondroblastoma replaces the proximal portion of the talus and is covered by the articular cartilage. The tumor is lobular, tan-white, and has well-circumscribed margins* ➔.

### Chondroblastoma in Metaphysis



### Irregular Tumor in Patella

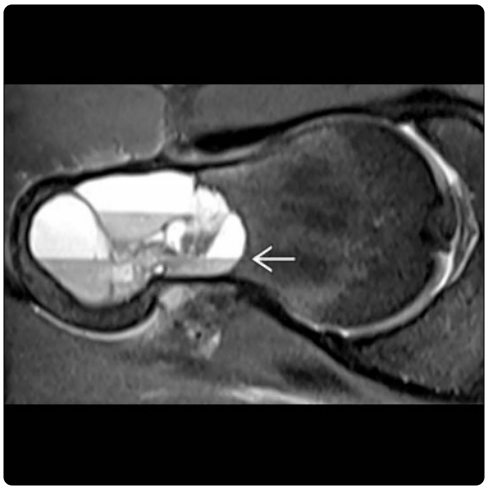


**(Left)** *AP view of the knee shows an oval-shaped tumor* ➔ *with a thin, sclerotic margin in the medial tibial metaphysis. The oval mass contains multiple spiculated radiodensities. There is no periosteal reaction, and the other osseous structures are unremarkable.* **(Right)** *Chondroblastoma is one of the more common tumors that affects the patella. In this case, the lesion is lytic and has well-circumscribed margins and an irregular configuration.*

### Pathologic Fracture Through Tumor



### Fluid-Fluid Levels

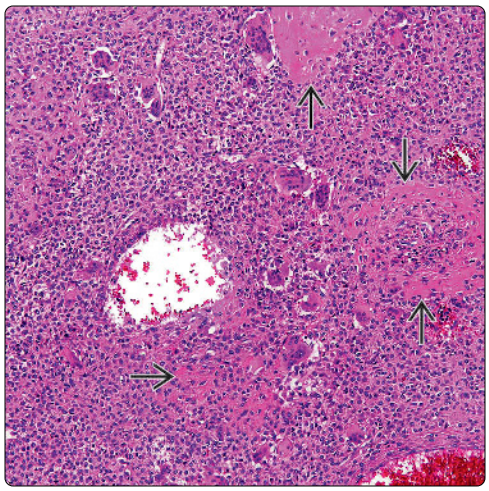


**(Left)** *A lytic lesion is seen in the proximal humerus* ➔ *extending into the metaphysis. No internal matrix is visible. There is a pathologic fracture through the lesion. Soft tissue swelling is noted.* **(Right)** *Chondroblastoma is one of the few primary bone tumors that undergo secondary hemorrhagic cystic change that can resemble a chondroblastoma. In this level of the tumor, prominent fluid-fluid levels* ➔ *are present.*

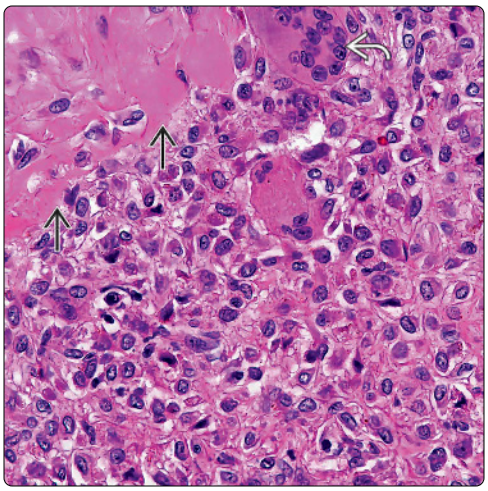


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### Chondroblastoma With Eosinophilic Matrix

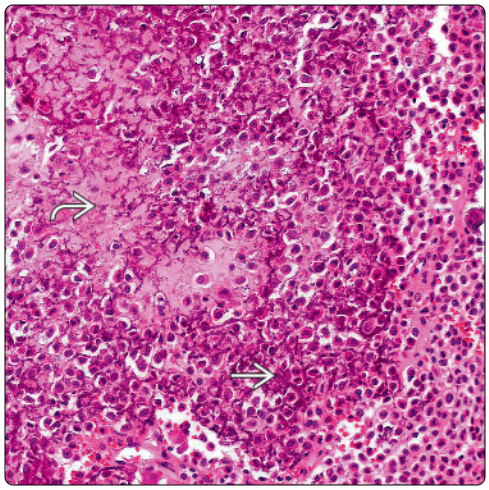


### Eosinophilic Matrix

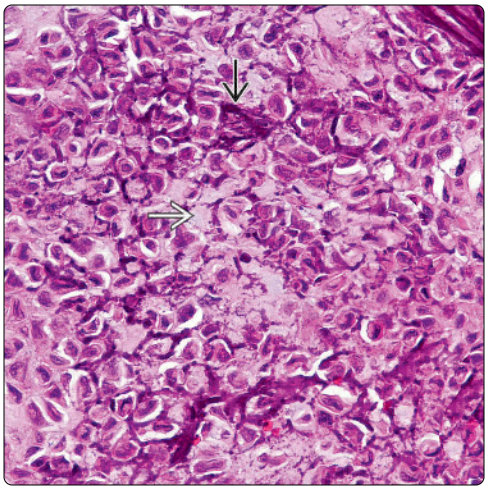


**(Left)** *Chondroblastoma is shown with a small cystic component. The densely cellular tumor contains islands of eosinophilic matrix. Multinucleated osteoclast-type giant cells are present in small groups in areas of the tumor.* **(Right)** *Chondroblastoma is shown with a fibrillar eosinophilic matrix. The matrix can resemble bone, and an osteoclast is adjacent to its surface. The chondroblasts grow in a solid cellular sheet and have eosinophilic cytoplasm and oval vesicular nuclei.*

### Chicken-Wire-Like Calcifications

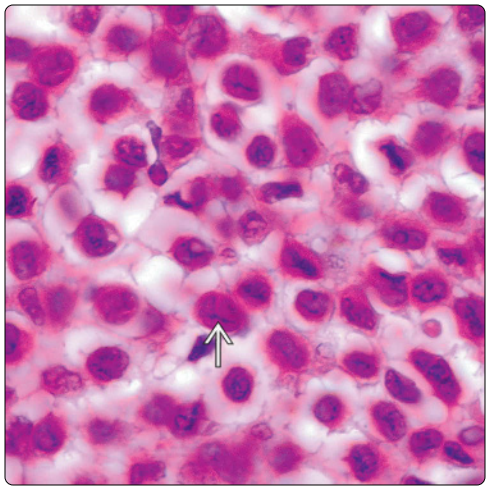


### Chicken-Wire-Like Calcifications

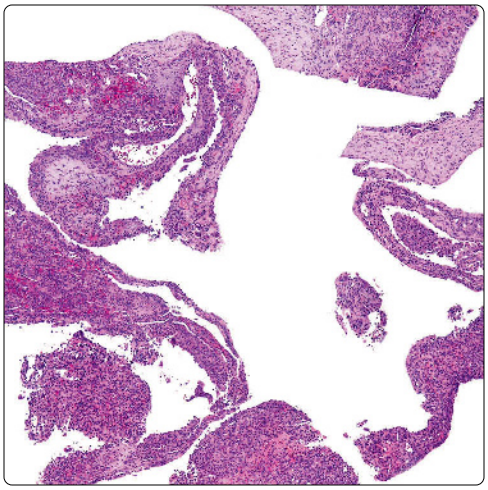


**(Left)** *Chondroblastoma shows extensive calcification (purple) of the poorly formed hyaline matrix that surrounds individual tumor cells. This pattern of mineralization is chicken-wire-like in configuration. Areas of cell necrosis are present.* **(Right)** *Chicken-wire-like calcification of basophilic, poorly formed hyaline matrix appears purple in nondecalcified tissue as seen here. The matrix and calcifications surround individual chondroblasts and are typical of chondroblastoma.*

### Cytologic Features of Chondroblastoma



### Cystic Changes in Chondroblastoma

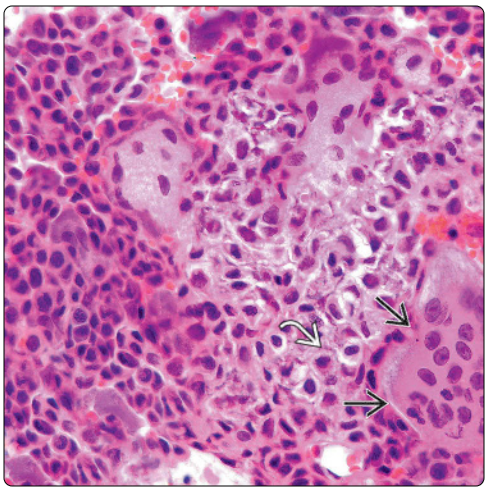


**(Left)** *Sheets of chondroblasts form a cobble stone appearance in chondroblastoma. Polyhedral cells are moderate in size with well-delineated cytoplasmic membranes and eosinophilic cytoplasm. Oval nuclei are cleaved, hyperlobated, and resemble those of Langerhans cells.* **(Right)** *Chondroblastoma, which underwent extensive cystic change, is seen. This change can mimic an aneurysmal bone cyst; only small foci of diagnostic chondroblastoma may be present in cyst walls.*

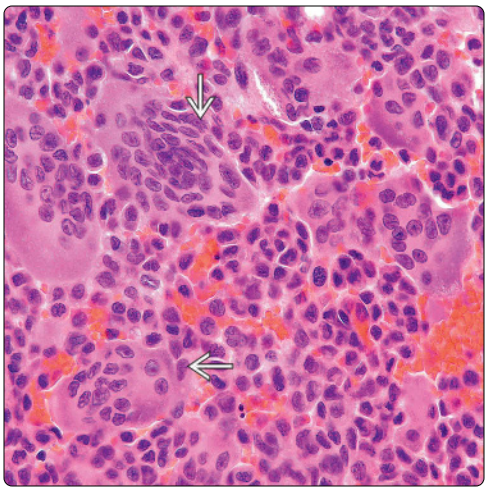


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### Chondroblastoma With Giant Cells

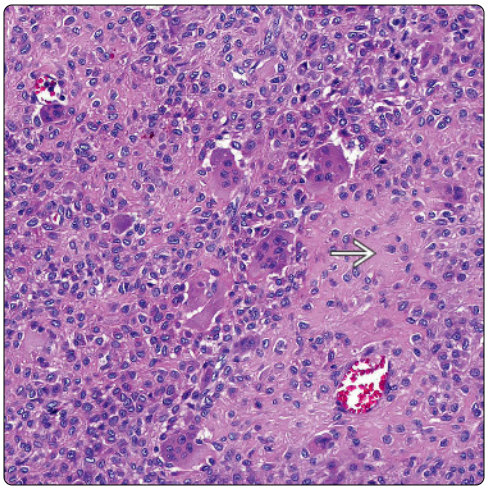


### Numerous Giant Cells

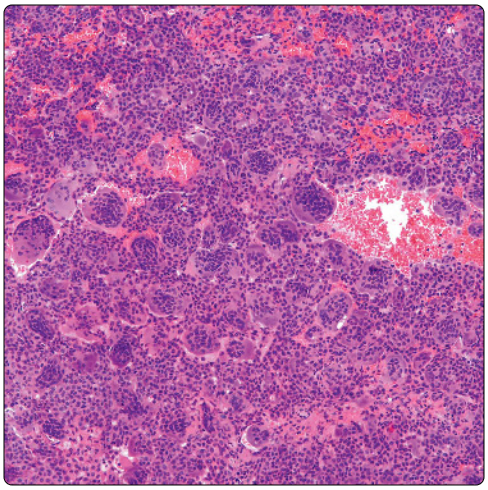


**(Left)** *Chondroblastoma containing sheets of chondroblasts is associated with an extracellular matrix, which is focally calcified. The polyhedral chondroblasts have irregular convoluted nuclear contours. Also present are multinucleated osteoclast-like giant cells.* **(Right)** *Chondroblastoma containing numerous large osteoclast-like multinucleated giant cells mimics a giant cell tumor of bone. The chondroblasts grow in sheets and are admixed with extravasated red blood cells.*

### Eosinophilic Extracellular Matrix

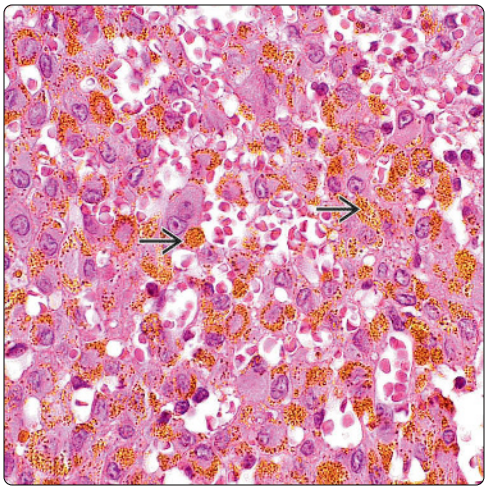


### Numerous Giant Cells

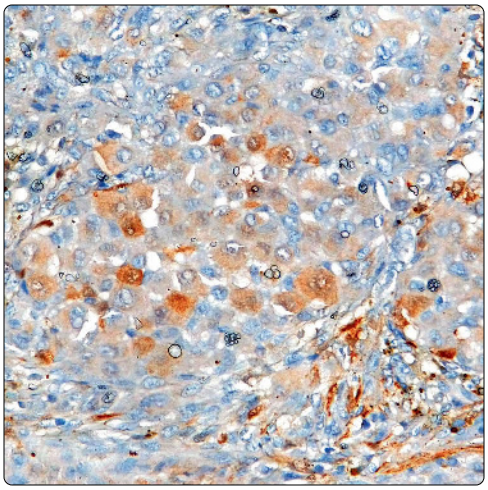


**(Left)** *This chondroblastoma is composed of numerous mononuclear cells and scattered osteoclast-type giant cells. Extracellular eosinophilic (pink chondroid) matrix is present.* **(Right)** *This chondroblastoma is cellular with numerous large osteoclast-type giant cells mimicking a giant cell tumor of bone.*

### Hemosiderin Deposition



### S100 Stain



**(Left)** *Chondroblastomas of the head and neck often have chondroblasts that contain abundant intracytoplasmic hemosiderin pigment, which can mimic a tenosynovial giant cell tumor.* **(Right)** *Chondroblastoma of temporal bone expresses S100. Chondroblastoma of temporal bone can be confused with a tenosynovial giant cell tumor, and immunohistochemistry is helpful because the tumor cells in a tenosynovial giant cell tumor are S100 negative.*



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# Chondromyxoid Fibroma

KEY FACTS

## CLINICAL ISSUES

- One of least common neoplasms of bone; < 1% of all primary bone tumors
- Arises in patients in 2nd-3rd decades of life
- ~ 1/2 of cases involve long tubular bones
- Curettage is most common therapy
- Conservative en bloc resection
- Local recurrence rate ~ 20%

## IMAGING

- Eccentric and radiolucent, well-circumscribed margins
- Multiloculated lesion in metaphysis; long axis of tumor parallels long axis of bone
- May contain small calcifications

## MACROSCOPIC

- Ranges in size from 1-10 cm, well circumscribed, tan-white, and rubbery

## MICROSCOPIC

- Well defined, lobulated
- Composed of relatively hypocellular chondroid or chondromyxoid tissue that is more cellular peripherally
- Cells in cartilaginous areas stain for S100 protein; peripheral cellular regions express muscle-specific and smooth muscle actin but not S100 protein
- Often vascular with vessels having branching staghorn pattern

## TOP DIFFERENTIAL DIAGNOSES

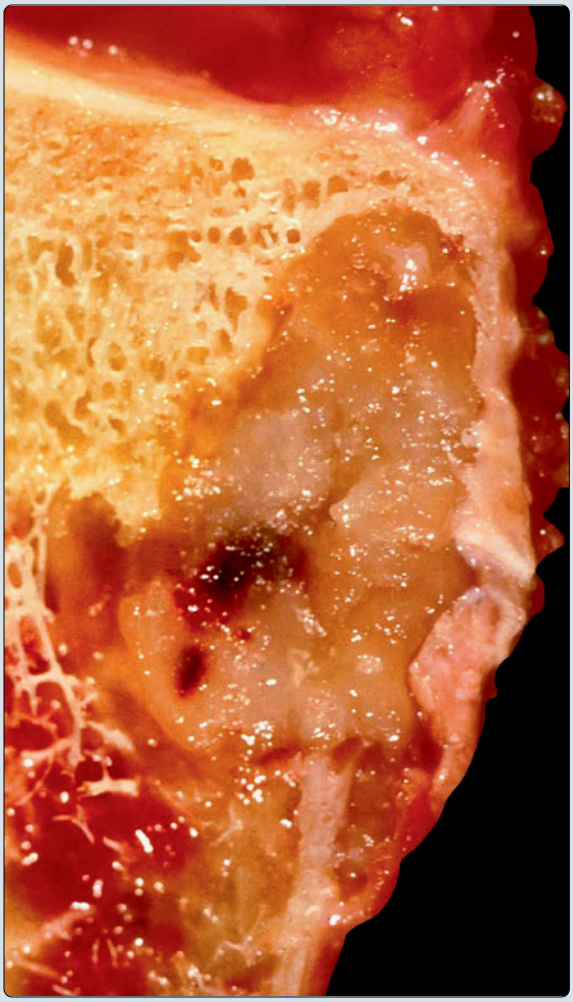
- Chondroblastoma
- Enchondroma
- Low-grade chondrosarcoma
- Chondromyxoid fibroma-like osteosarcoma
- Fibromyxoma
- Osteochondromyxoma

**Large Tumor in Young Patient**



*Anteroposterior radiograph shows a radiolucent, lobulated lesion in the tibial metadiaphysis exhibiting a geographic type of bone destruction, sclerotic scalloped borders, and internal septa. The tumor is arising in a skeletally immature individual with an open growth plate.*

**Lobulated Gelatinous Tumor**



*Chondromyxoid fibroma (CMF) is typically well demarcated, tan, and glistening. The solid tumor has a lobular architecture, expands the cortex, and is covered by a rim of periosteal new bone.*



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## TERMINOLOGY

### Definitions

- Benign cartilaginous neoplasm, characterized by lobules of stellate or spindle-shaped cells embedded in abundant extracellular myxoid or chondroid matrix

## ETIOLOGY/PATHOGENESIS

### Unknown

- Likely results from mutations in mesenchymal stem cells

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Uncommon neoplasm of bone
    - Incidence is 0.48 per million inhabitants (Netherlands) between ages of 0-18 years; accounts for < 1% of all primary bone tumors and < 2% of benign bone tumors
- Age
  - Develop during 2nd-3rd decades of life (50% of patients); 72% are younger than 40 years
- Sex
  - Males are affected slightly more frequently than females

### Site

- Majority of cases arise in medullary cavity and are often eccentric
- ~ 1/2 of cases involve metaphysis of long tubular bones, usually around knee
- ~ 30% of cases arise in flat bones: Ilium (45%), ribs (26%), vertebrae (8%), scapula (2%)
- Bones of feet involved in 15% of cases; metatarsals more frequently affected than phalanges
- Bones of hand are involved in 3% of cases; craniofacial skeleton in 5%

### Presentation

- Pain; may be present for long duration; swelling
- Incidental finding on x-rays; rarely associated with oncogenic osteomalacia

### Treatment

- Depends on location of tumor
  - Curettage and packing with bone chips or bone cement
  - Conservative en block resection
  - Tumors located in critical sites, such as skull base, may require radiation

### Prognosis

- Local recurrence rate is ~ 20%
  - Predominantly occurs in tumors treated by curettage
  - Multiple recurrences uncommon and should raise suspicion of chondrosarcoma
  - Recurrence develops after 5-120 months
  - No relationship between recurrence and histologic appearance
- Rare examples of malignant chondromyxoid fibroma and sarcomatous transformation have been reported
  - Some of these examples have followed radiation therapy

## IMAGING

### Radiographic Findings

- In long bones, tumors are metaphyseal and eccentric
  - 88% involve metaphysis; 68% are purely metaphyseal
  - Rarely restricted to diaphysis or epiphysis
  - Long axis of tumor parallels long axis of bone
- In short tubular bones, tumor involves metaphysis in 84% of cases; 42% affect metaphysis and epiphysis
- Radiolucent
  - 13% show scattered irregular spiculated calcifications
- Commonly causes cortical thinning and expansion
  - Complete resorption of portion of cortex may occur with focal extension into soft tissue
- Multiloculated with lobular contour and internal septa; margins of lesion are sharp and frequently have sclerotic rim
- Periosteal reaction is unusual; pathologic fracture is very uncommon

### MR Findings

- Well-delineated tumor; T1-weighted images show low to intermediate signal intensity; T2-weighted images show high signal intensity

### CT Findings

- Well-defined lytic lesion; minority show internal matrix calcifications; covered by thin layer of thinned cortex

### Bone Scan

- Increased uptake of radiotracer

## MACROSCOPIC

### General Features

- Solitary, solid, lobulated; well circumscribed; tan-white, firm, and glistening; gritty when calcified

### Sections to Be Submitted

- Curettage specimens
  - Entire tumor up to 10 cassettes
- Resection specimens
  - 1 section per centimeter of greatest dimension of tumor and resection margins

### Size

- Ranges from 1-10 cm

## MICROSCOPIC

### Histologic Features

- Well-defined margins
  - Infrequently permeates trabecular bone
    - e.g., metatarsals, cranium
- Lobulated contour and architecture
  - Center of lobules relatively hypocellular with increase in cellularity toward periphery
- Stellate or spindle-shaped cells with abundant myxoid or chondroid matrix
- In chondroid areas, cells are oval and reside within lacunae surrounded by poorly formed hyaline cartilage-like matrix
- Well-developed hyaline cartilage is present in ~ 20% of tumors and is not extensive



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- Most prominent in lesions of small bones of hands and feet
- Myxoid areas composed of stellate cells enmeshed in frothy basophilic matrix
- Hypercellular peripheral regions may contain scattered multinucleated osteoclast-type giant cells and sheets of polyhedral cells resembling chondroblasts
  - Chondroblast-like cells have cleaved and hyperlobated nuclei
- Mitoses are relatively uncommon and are of normal configuration
- Coarse deposits of calcium within chondroid matrix are present in ~ 20-35% of cases
  - Deposits are oval, clumped or plaque-like, dense, and purple on H&E-stained slides
- Pseudomalignant cells present in minority of tumors
  - These cells are mitotically inactive but have enlarged, hyperchromatic, pleomorphic, and vacuolated nuclei
  - Similar to those present in ancient schwannoma
- Fibrous component includes septa that compartmentalize tumor into lobules
- Frequently contains small, thin-walled branching vessels that have hemangiopericytoma-like growth pattern
  - Most cartilage tumors lack prominent vascular tree
- Aneurysmal bone cyst-like changes can be seen in ~ 10% of tumors

## ANCILLARY TESTS

### Immunohistochemistry

- Cells in cartilaginous areas and sometimes myxoid regions stain for S100 protein
- Cells in peripheral cellular regions express muscle-specific and smooth muscle actin but not S100 protein
- Matrix of chondromyxoid fibroma contains collagen types I, II, III, and VI as well as hydrated proteoglycans
  - Composition seems to be specific for chondromyxoid fibroma
    - Has not been found in other cartilaginous tumors, such as chondroblastoma, osteochondroma, enchondroma, or chondrosarcoma
- SOX9 stains nuclei of stellate and spindle-shaped cells
- Nuclear ERG expression is seen in chondromyxoid fibroma as in many other chondroid neoplasms

### Genetic Testing

- Clonal rearrangement of chromosome 6, involving bands q13 and q25
- Recent study suggests that glutamate receptor gene (*GRM1*) appears to be necessary and specific driver for development of chondromyxoid fibroma

### Electron Microscopy

- Cells in chondroid regions have features of chondrocytes
- Cells in peripheral regions show myofibroblastic and myochondroblastic differentiation

## DIFFERENTIAL DIAGNOSIS

### Chondroblastoma

- Arises in younger patients who are often skeletally immature; centered in epiphysis and not in metaphysis as in chondromyxoid fibroma
- Lacks prominent lobulated architecture
- Cellular regions of chondromyxoid fibroma can be histologically very similar to chondroblastoma
- Contains chicken-wire-like calcifications rather than globular deposits of mineral seen in chondromyxoid fibroma

### Enchondroma

- Composed of well-formed hyaline cartilage; nodules of mature-appearing hyaline cartilage uncommon in chondromyxoid fibroma
- Cartilage undergoes enchondral ossification
  - This finding is rare in chondromyxoid fibroma

### Low-Grade Chondrosarcoma

- Lacks lobulated architecture seen in chondromyxoid fibroma
- Less cellular and fewer blood vessels
- Shows infiltrative growth pattern
- Radiographically demonstrates more aggressive appearance

### Chondromyxoid Fibroma-Like Osteosarcoma

- Radiographically more aggressive with poorly defined margins
- Shows more cytologic atypia and infiltrative growth pattern
- Neoplastic cells can express S100

### Fibromyxoma

- Rare bone tumor that has some histologic similarities to chondromyxoid fibroma, and some believe it is variant thereof

### Osteochondromyxoma

- Very rare congenital bone tumor that has some histologic similarities to chondromyxoid fibroma
- Associated with Carney complex

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Think chondromyxoid fibroma when eccentrically located, well-defined metaphyseal lytic tumor is seen in skeletally mature individual

### Pathologic Interpretation Pearls

- Margins of growth are well defined; low-power architecture is distinctly lobulated
- Composed of chondroid areas with myxoid and fibrous tissue; fibrous areas often have branching blood vessels that are hemangiopericytoma-like in appearance
- Pseudomalignant features may be present

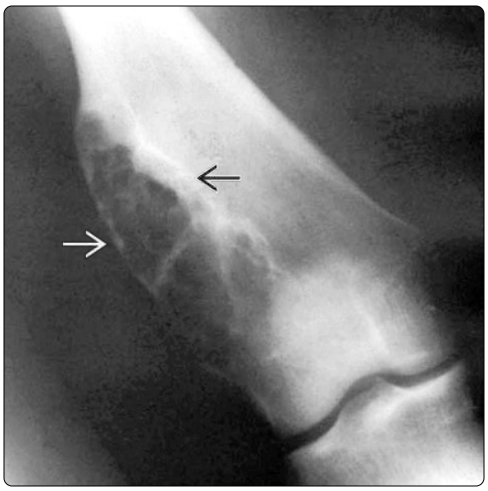
## SELECTED REFERENCES

1. Wu CT et al: Chondromyxoid fibroma of bone: a clinicopathologic review of 278 cases. Hum Pathol. 29(5):438-46, 1998



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Eccentric Lytic Tumor



Well-Demarcated Tumor



**(Left)** *Radiograph shows a typical CMF of the distal femur, which is centered in the metaphysis and eccentrically situated in the bone. It is delineated by a thin but well-formed sclerotic boundary* ⇨ *and layer of subperiosteal new bone* ➡. **(Right)** *Coronal T1-weighted MR of CMF demonstrates the nodular soft tissue component of the lesion. The tumor appears solid, well demarcated, and may have arisen within the lateral femoral cortex.*

Small Chondromyxoid Fibroma



Well-Circumscribed Mass



**(Left)** *Radiograph shows a small, eccentrically located oval lesion* ⇨ *arising in the metaphysis of the distal femur. The tumor has a lobular contour and a thin sclerotic boundary.* **(Right)** *CT scan of a CMF* ➡ *of the femur shows that the long axis of the lesion is transverse to the bone and follows the contour of the adjacent cortex. The tumor appears to have arisen eccentrically in the medullary cavity or from the endosteal surface of the anterior cortex.*

Juxtacortical Mass



Surface Chondromyxoid Fibroma

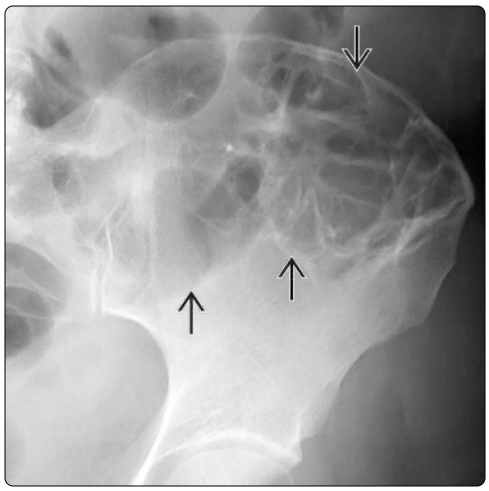


**(Left)** *Radiograph of the tibia shows a surface lesion unusual for CMF. The lytic, oval lesion has adjacent reactive bone at its margin* ➡. *Other benign surface lesions in the differential diagnosis include chondroma, hemangioma, and osteoblastoma.* **(Right)** *Sagittal T2-weighted MR of a surface CMF* ➡ *of the tibia displaces the overlying tissues. The well-circumscribed tumor has a high signal intensity corresponding to high water content.*



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**Large Lytic Tumor of Ilium**



**Trabeculated Appearance of Tumor**



**(Left)** *AP radiograph of the pelvis shows a large, lobulated, septated CMF ⇨ of the iliac bone. The lytic tumor is well demarcated and is surrounded by a thin rim of sclerotic bone.* **(Right)** *Axial CT scan shows a CMF arising in the medullary cavity of the iliac bone that has sustained a pathological fracture ⇨. Enhancing fibrous septations ➡ partition the mass into lobules. The tumor extends into the soft tissues ➡.*

**Multinodular Tumor in Fibula**

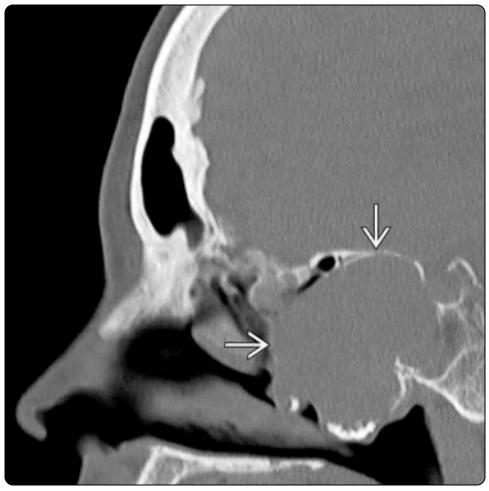


**Expansile Lytic Mass**

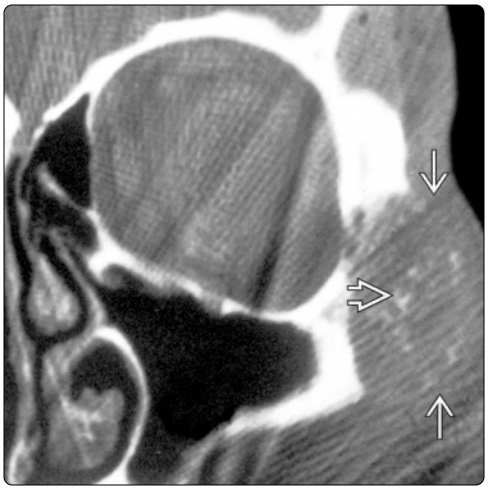


**(Left)** *Plain radiograph shows a CMF arising in the metaphysis of the proximal fibula. The lytic, well-delineated, oval tumor has a soap bubble-like appearance and has eroded the lateral cortex ➡. Note the periosteal reaction distal to the mass ⇨.* **(Right)** *Eccentric and expansile CMF arises in the metaphysis of the metatarsal in a skeletally immature patient. A lobular architecture is less apparent, but a well-formed sclerotic boundary is present ⇨.*

**Large Tumor of Skull Base**



**Skull Base Chondromyxoid Fibroma**



**(Left)** *Sagittal CT scan shows a CMF arising within the sphenoid ➡. The tumor is well defined and has an expansile contour, suggesting that it may be slow growing or benign, but it has completely destroyed the anterior cortex of the sinus.* **(Right)** *A coronal CT scan shows a surface lesion arising from the zygoma ➡. Calcifications ➡ suggestive of cartilage are present. This feature is rare in CMF and is much more typical of chondroma and chondroblastoma.*

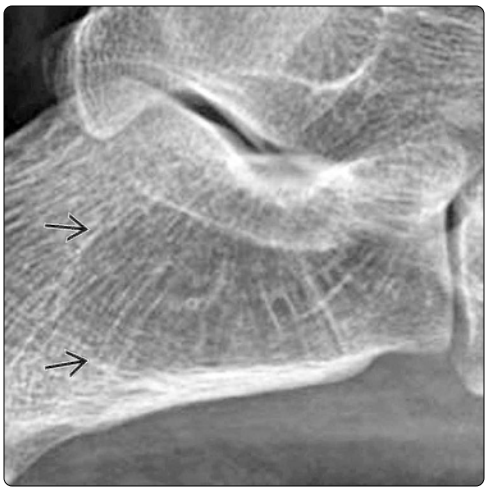


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### Recurrent Chondromyxoid Fibroma

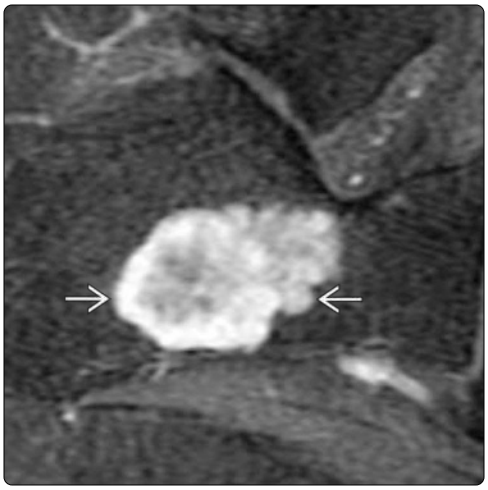


### Lytic Mass With Sharp Margin

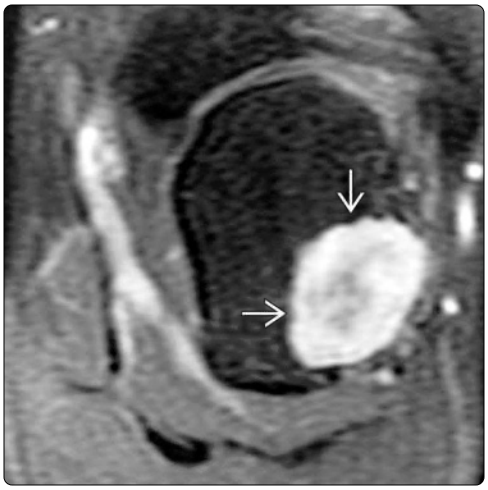


**(Left)** *A radiograph shows a recurrent CMF of the tibia following curettage and packing with bone. The recurrent tumor manifests as multiple, oval, lytic lesions that are peripheral to the bone packing.* **(Right)** *A lateral radiograph of the ankle shows a lucent lesion in the calcaneus. The tumor is well circumscribed and has a subtle sclerotic rim.*

### Bright Tumor

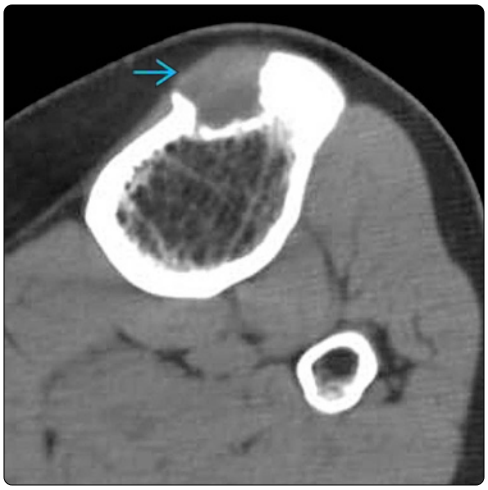


### Eccentric, Well-Circumscribed Tumor



**(Left)** *A sagittal T2-weighted MR with fat saturation demonstrates a lobulated, hyperintense lesion in the calcaneus extending to the inferior cortex of the bone.* **(Right)** *A coronal T2-weighted MR with fat saturation shows a lobulated, hyperintense lesion in the calcaneus extending to and expanding the lateral cortex of the bone.*

### Intracortical Lytic Tumor



### Large Tumor in Metaphysis

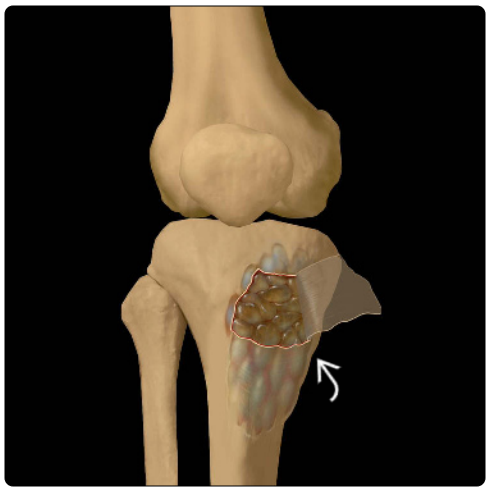


**(Left)** *A cortically based CMF in the proximal tibia is shown. The tumor is well circumscribed and does not involved the underlying medullary cavity of the bone. The lucent area is probably from the mucoid tissue.* **(Right)** *A CMF arising in a skeletally immature individual with open growth plates is shown. The tumor is arising in the distal femur, is lobulated, septated, and metaphyseal in location. The lesion has expanded and deformed the bone.*

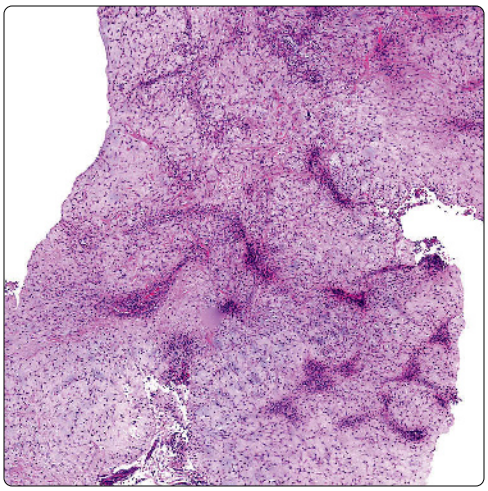


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**Chondromyxoid Fibroma**

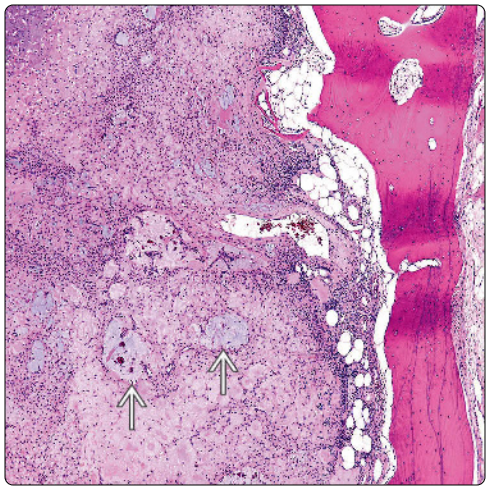


**Needle Biopsy**

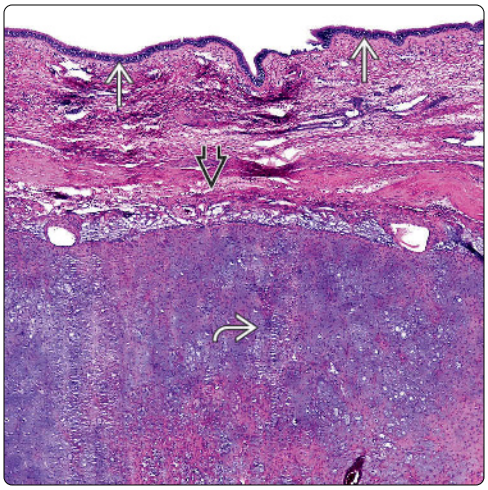


**(Left)** *Graphic depicts the gross pathologic appearance of CMF. The lesion is well demarcated and has a glistening fleshy appearance. It is eccentrically located and results in mild expansion of the cortex.* **(Right)** *Needle core biopsy of a CMF demonstrates a vaguely lobular growth pattern. The tumor contains branching capillaries and prominent myxoid and fibrous areas.*

**Periphery of Chondromyxoid Fibroma**

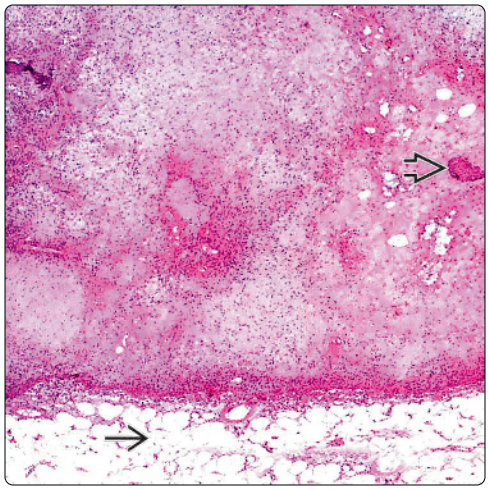


**Skull Base Tumor**

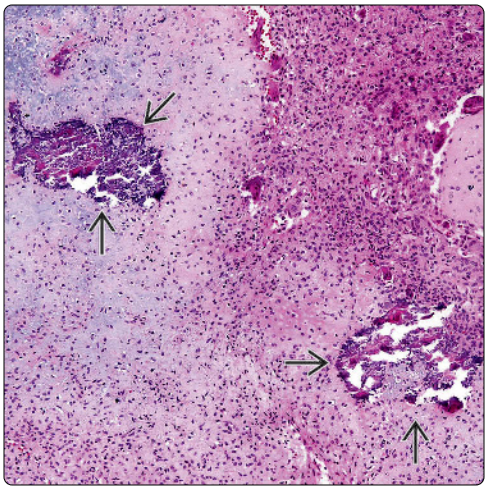


**(Left)** *Periphery of CMF shows sharp margins with the adjacent thinned cortex. The tumor has a lobular architecture and varies in its cellularity. The tumor has prominent chondromyxoid components with scattered small islands of chondroid tissue.* **(Right)** *A CMF of the skull base is shown displacing the sinonasal mucosa. The tumor is lobulated, well demarcated, and covered by a layer of periosteum.*

**Well-Demarcated Margin**



**Coarse Calcifications**

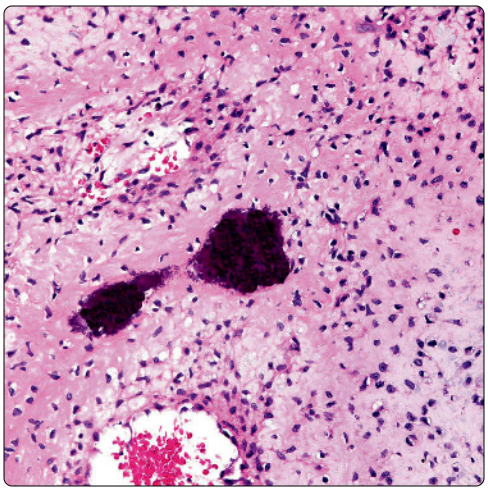


**(Left)** *Intramedullary margin of a CMF shows a well-demarcated border with the adjacent marrow fat. The tumor has a lobular architecture and varies in the degree of cellularity. Small calcifications are present.* **(Right)** *CMF is lobulated and composed of blue chondroid areas separated by cellular areas. Note the coarse calcifications in the chondroid areas.*

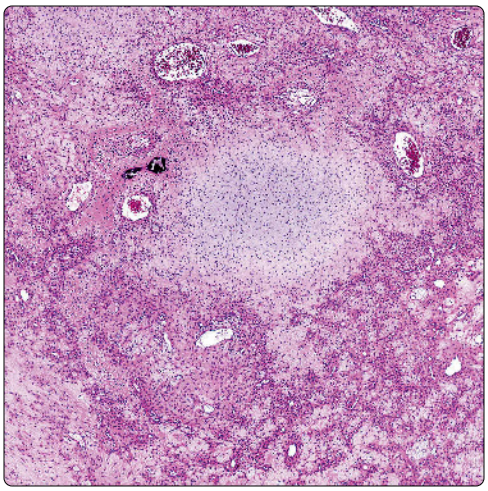


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### Dense Calcifications

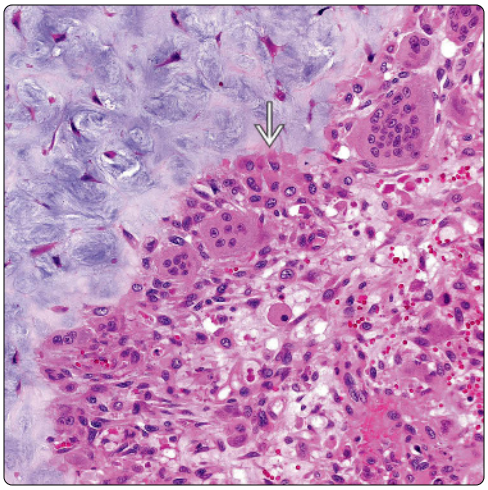


### Chondroid Area

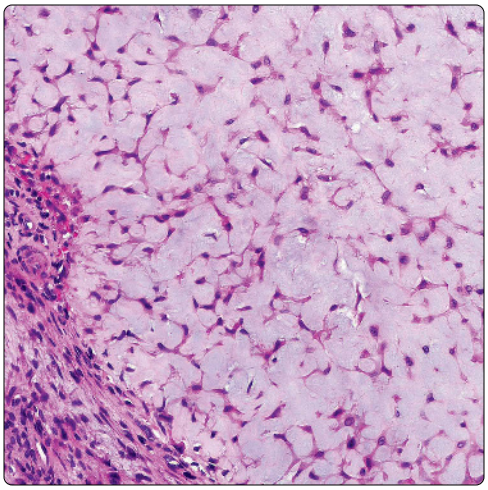


**(Left)** *CMF shows characteristic coarse purple calcifications, which are seen in ~ 20% of cases. The calcifications are occurring in the chondroid region. Note the prominent blood vessels.* **(Right)** *CMF with a central portion contains a chondroid nodule with a prominent bluish matrix. The surrounding area is cellular and contains numerous blood vessels.*

### Chondroblastoma-Like Area

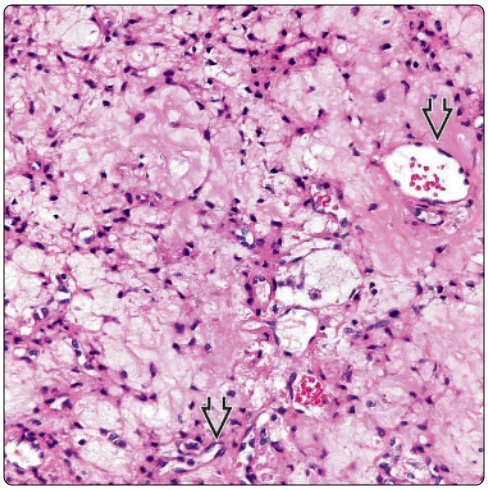


### Myxoid Area

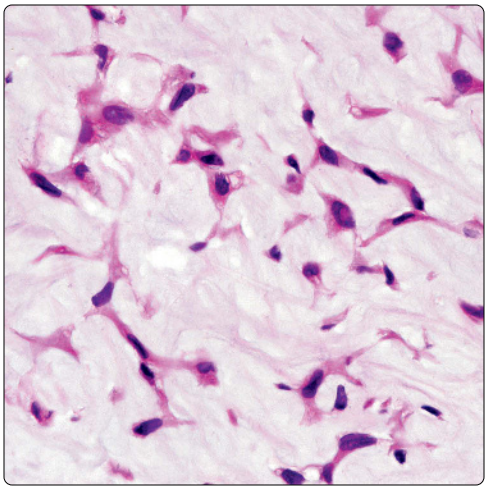


**(Left)** *CMF shows the junction of a chondroid area and an adjacent hypercellular area. The chondroid area is composed of stellate cells embedded in a blue matrix, which is rimmed by osteoclasts. The mononuclear cells resemble those in chondroblastoma* ⇨. **(Right)** *CMF is shown with a myxoid area containing bland spindle- and stellate-shaped cells with oval dark nuclei and eosinophilic cytoplasm. The cytoplasmic processes extend from the cell bodies to form a complex interconnecting network.*

### Myxoid Region of Stroma



### Spindle and Stellate Cells



**(Left)** *Myxoid area of CMF is shown with scattered stellate cells and abundant edematous stroma. The branching blood vessels are prominent* ⇨ *and focally dilated.* **(Right)** *Cells in the myxoid areas are spindle- or stellate-shaped with centrally located nuclei with finely dispersed or homogeneous dark chromatin and eosinophilic cytoplasm. Extracellular matrix is myxoid and basophilic. Mitotic activity is usually very low.*



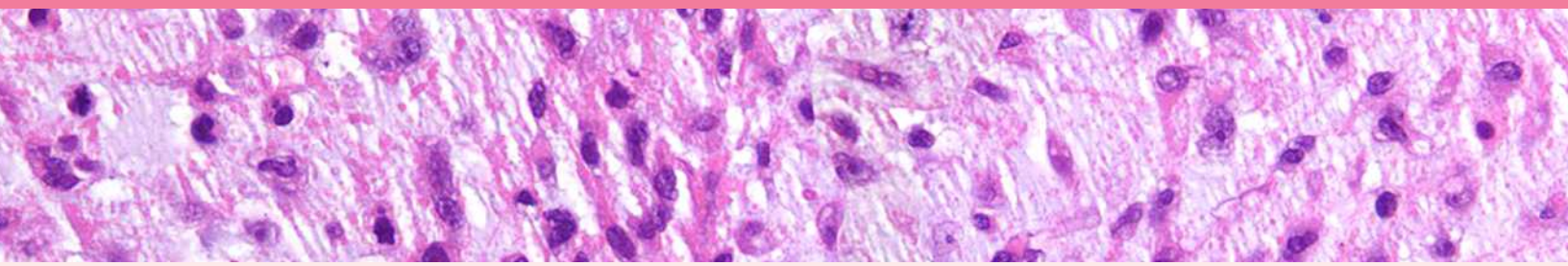
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SECTION 4

# Malignant Cartilage Tumors




| | |
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| Conventional Chondrosarcoma | **138** |
| Dedifferentiated Chondrosarcoma | **150** |
| Clear Cell Chondrosarcoma | **156** |
| Mesenchymal Chondrosarcoma | **162** |

# Conventional Chondrosarcoma

KEY FACTS

## TERMINOLOGY

- Malignant cartilaginous matrix-producing tumor
- Secondary chondrosarcoma (CSA) arises in association with preexisting benign tumor or diseased bone
- Periosteal CSA arises on bone surface

## CLINICAL ISSUES

- Conventional intramedullary CSA accounts for > 90% of all CSAs
- CSAs arising in osteochondroma and periosteal CSA are rare
- Primary CSA usually develops in adults in 5th-7th decades of life
- Can arise in any bone derived from endochondral ossification
- Most originate in pelvis and femur
- Patients usually present with pain or enlarging mass

## IMAGING

- Intramedullary and radiolucent with scattered radiodensities
- Densities often take form of rings, arcs, and irregular spiculations
- MR is helpful in identifying extent of tumor preoperatively

## MACROSCOPIC

- Neoplastic hyaline cartilage is gray-tan and glistening

## MICROSCOPIC

- Infiltration of preexisting bone is important histologic finding and distinguishes CSA from benign cartilaginous tumor

## TOP DIFFERENTIAL DIAGNOSES

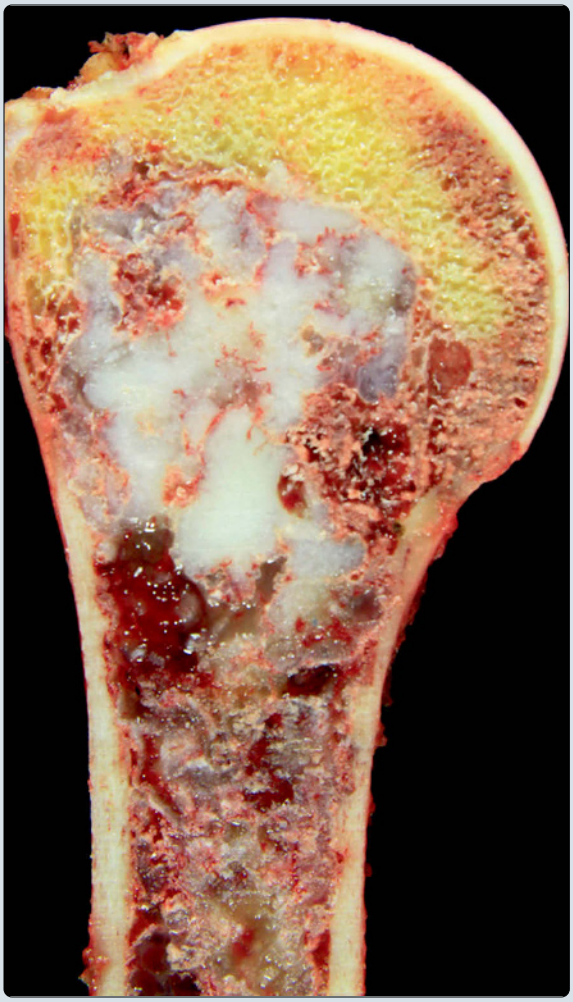
- Enchondroma, chondromyxoid fibroma, clear cell CSA
- Chordoma
- Fracture callus

**Chondrosarcoma Arising in Enchondroma**



*In the proximal humerus, the tumor demonstrated the typical mineralization for enchondroma with the rings and arches. The more distal portion of the tumor is more lucent and less mineralized and represents the low-grade chondrosarcoma (CSA) arising in this enchondroma.*

**Chondrosarcoma Arising in Enchondroma**



*The proximal portion of the tumor is composed of nodules of hyaline-type cartilage representing the enchondroma, while the distal portion is more gelatinous, which represents the low-grade CSA*



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## TERMINOLOGY

### Abbreviations

- Chondrosarcoma (CSA)

### Definitions

- Malignant cartilaginous matrix-producing tumor
- Primary CSA arises in normal bone
- Secondary CSA arises in association with
  - Preexisting benign tumor
    - Enchondroma/enchondromatosis, osteochondroma, fibrous dysplasia
  - Diseased bone
    - Radiation, Paget disease
- Periosteal CSA arises on surface of bone
  - a.k.a. juxtacortical CSA
- In WHO classification of bone tumors, low-grade CSA is classified under "intermediate (locally aggressive)" as "atypical cartilaginous tumor/CSA grade 1," as it is often very difficult to distinguish between cellular enchondroma and grade 1 CSA

## ETIOLOGY/PATHOGENESIS

### Neoplastic

- Etiology for most CSAs is unknown
- In some CSAs, one can find preexisting enchondroma(s)
  - Likely represents malignant transformation from enchondroma
  - Risk of malignant transformation of sporadic enchondroma is very low (< 1%)
- Patients with enchondromatosis, such as Ollier disease or Maffucci syndrome, have increased risk of developing CSA
  - Risk of malignant transformation is 35-40%
- Patients with osteochondromatosis have 5-25% chance of developing CSA
- CSA very rarely arises in patients with solitary osteochondroma
  - Estimated incidence is 0.4-2.0% but is probably lower

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Primary CSA is 2nd most common primary malignant bone tumor after osteosarcoma
    - Accounts for ~ 20% of malignant bone tumors
  - Conventional intramedullary CSA accounts for > 90% of all CSAs
- Age
  - Primary CSA usually develops in adults in 5th-7th decades of life
    - Very rare in children; in this age group, chondroblastic osteosarcoma should be excluded
- Sex
  - Males affected slightly more frequently than females

### Site

- Can arise in any bone derived from endochondral ossification
- Most originate in pelvis, especially ilium
  - Followed by proximal femur, proximal humerus, distal femur, and ribs
    - In long bones, CSA usually involves metaphysis or diaphysis
- Infrequently develops in small bones of hands and feet (1% of CSA)
- CSAs of cranium usually involve skull base, where bones are formed by endochondral ossification
- Most CSAs arising in osteochondroma originate in pelvis or femur
- Periosteal CSAs most commonly involve distal femur

### Presentation

- Patients present with pain, enlarging mass, and, infrequently, fracture
  - Symptoms often present for long time
- Skull base tumors frequently cause headache, diplopia, and cranial nerve palsies
- In patients with osteochondroma(tosis), any change in clinical symptoms or increase in size after puberty should raise suspicion of malignant transformation

### Treatment

- Aggressive curettage for low-grade (grade 1/3) CSAs
  - Especially if tumor is located in appendicular skeleton
- High-grade CSA (grades 2/3 and 3/3) require wide surgical resection
- Radiation has been used to treat unresectable tumors
  - Frequently used for tumors arising in spine or skull base
- CSAs arising in pelvis are treated with resection regardless of grade because local recurrence in this region is very difficult to treat

### Prognosis

- Histologic grade is single most important prognostic factor
- Grade 1 CSAs behave in locally aggressive manner
  - Deaths usually result from local recurrence
  - Metastases are very rare
  - 5-year survival for grade 1 CSA is ~ 85%
- Grades 2 and 3 CSA have much worse prognosis
  - 5-year survival rate is ~ 50%
- Recurrent tumors may have increase in histologic grade
- Prognosis for secondary intramedullary CSA arising in enchondroma or enchondromatosis is same as for primary CSA and depends on grade of tumor
- Prognosis of CSA arising in osteochondroma is excellent unless there is dedifferentiation
- Periosteal CSAs tend to recur locally
  - Metastases are rare

## IMAGING

### Radiographic Findings

- Lytic with scattered radiodensities
- Densities often take form of rings and arcs and irregular spiculations
  - Rings and arcs represent peripheral enchondral ossification and reactive bone formation
  - Spiculations caused by irregular calcification of matrix
- Low-grade tumors may have significant areas of mineralization, produce bone expansion, endosteal scalloping, and thickening of cortex



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- High-grade tumors have large radiolucent areas and cortical destruction, frequently with significant soft tissue mass
- Permeation of cortex rarely seen
  - Except in most aggressive lesions
- Periosteal CSA shows irregular mineralization on surface of bone

### MR Findings

- MR is helpful in identifying extent of tumor
- Dark on T1-weighted images
- Bright on T2-weighted images
- In osteochondroma, cartilage cap with thickness of > 1.5-2.0 cm should raise suspicion of possible malignant transformation
  - Thickened cap is not diagnostic for malignancy
- In periosteal CSA, there is T2-bright mass arising on surface of bone with areas of mineralization

### CT Findings

- Unmineralized and mineralized components of tumor are clearly delineated in intramedullary and surface lesions

### Bone Scan

- Avid technetium uptake on bone scan

## MACROSCOPIC

### General Features

- Low-grade tumors fill medullary cavity, expand bone, scallop endosteal surface, and produce cortical thickening
- High-grade tumors destroy cortex and form soft tissue mass that is frequently well delineated by raised periosteum
- Neoplastic hyaline cartilage is gray-tan and glistening
  - Has lobulated architecture that may be accentuated by thin fibrous septa
- Mineralized portions of matrix appear as scattered, punctuate, chalk-like deposits
- Regions of prominent endochondral ossification are seen as hard, ivory areas of bone formation
- Myxoid matrix is translucent, gray, and mucinous or watery
- In CSA arising in osteochondroma, cartilage cap is thick and frequently shows cystic changes
- In periosteal CSA, large (usually > 5 cm), gray, glistening mass is attached to surface of bone
  - It may contain gritty areas corresponding to calcification and ossification
  - Tumor scallops underlying cortex and can invade into medullary cavity

### Size

- Usually large (≥ 10 cm)

## MICROSCOPIC

### Histologic Features

- Infiltrative growth pattern encasing preexisting trabecular bone
- Neoplastic matrix is either hyaline or myxoid
  - Fibrocartilage is rare and elastic cartilage is not found
- Hyaline matrix is homogeneous and usually basophilic
  - Occasionally it may be pink
- Myxoid matrix is frothy or bubbly
  - Almost always basophilic
- Cartilage may mineralize or undergo endochondral ossification
- Neoplastic chondrocytes vary in size
  - Have moderate amounts of eosinophilic cytoplasm, occasionally vacuolated
- Tumor cells in hyaline cartilage are round to oval and confined to lacunar spaces
- Tumor cells in myxoid areas are bipolar or stellate and arranged singly or in cords and strands
  - Cytoplasmic processes of neighboring cells come in close or direct contact with one another and form complex cellular network
  - Tumor cells do not form tight cohesive nests or clusters
- Neoplastic cells demonstrate varying degrees of cytologic atypia
- May contain foci of enchondroma
- CSA arising in osteochondroma is usually low grade
  - Diagnosis of CSA in osteochondroma is subjective
    - Cartilage cap has nodular appearance with fibrous septa delineating lobules
    - Infiltration into stalk is unequivocal evidence of malignant transformation
- In periosteal CSA, hyaline-type cartilaginous tumor is seen on surface of bone
  - Usually low to intermediate grade with areas of calcification and ossification
  - Distinguishing periosteal chondroma from periosteal CSA is also often subjective
    - CSA shows more cellularity, atypia, invasion of underlying cortex, and, sometimes, infiltration into underlying medullary cavity

## ANCILLARY TESTS

### Genetic Testing

- Isocitrate dehydrogenase genes *IDH1* and *IDH2* are mutated in many CSAs
  - Primary CSA: 38-70%
  - Secondary CSA: 86%
  - Periosteal CSA: 100%
- Mutation analysis can be used in difficult cases to distinguish CSA from chondroblastic osteosarcoma in biopsy sample and to diagnose dedifferentiated CSA if no cartilage is seen on the biopsy

## DIFFERENTIAL DIAGNOSIS

### Enchondroma

- Does not grow with infiltrative pattern
- Relatively less cellular and lacks significant atypia

### Chondromyxoid Fibroma

- Has well-delineated margins
- Contains fibromyxoid tissue and abundant blood vessels
- Radiographically, chondromyxoid fibroma shows nonaggressive features and is well circumscribed
- Frequently contains osteoclast-type giant cells

### Clear Cell Chondrosarcoma

- Arises in epiphysis of long tubular bone, usually proximal femur and proximal humerus



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## Grading of Chondrosarcoma

| Grade | Cellularity | Cytologic Features |
|---|---|---|
| 1 | Hypocellular | Nuclei are small and dark or slightly enlarged with fine chromatin |
| 2 | More cellular | Nuclei are larger, irregular, and have coarse chromatin; mitoses infrequent |
| 3 | Hypercellular | Severe pleomorphism and mitoses |

## Enchondroma vs. Low-Grade Chondrosarcoma

| Enchondroma | Low-Grade Chondrosarcoma | Notes |
|---|---|---|
| Pain not attributed directly to neoplastic cartilage | Pain attributed to neoplastic cartilage | May be difficult to assess due to proximity of enchondromas to joints |
| Lack increased cellularity, double-nucleated chondrocytes, myxoid change, and chondrocyte necrosis | Increased cellularity, double-nucleated chondrocytes, myxoid change, and chondrocyte necrosis | Cytologic and histologic features may overlap; degree of overlap is even more apparent in patients with multiple endochondromas (endochondromatosis) |
| Absence of mitotic activity | Mitotic activity | Mitotic activity is extremely rare in enchondromas |
| Lack infiltrative growth pattern | Infiltrative growth pattern | This feature is diagnostic of low-grade chondrosarcoma |

- Contains clear cells, metaplastic bone formation, and osteoclast-type giant cells, features that are not present in conventional CSA

### Chordoma

- Chondroid chordomas can be difficult to differentiate from low-grade CSA
- Chondroid chordomas usually arise in skull base
- Immunohistochemically, chordomas stain with keratin and brachyury (not expressed by CSA)
  - Both tumors are S100 protein positive

### Fracture Callus

- On histologic features alone, fracture callus can easily be misdiagnosed as CSA
- Nodules of cartilage are small
- Cartilage undergoes endochondral ossification
- Should be easy to distinguish radiographically

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- On core biopsy, it can be impossible to differentiate between enchondroma and low-grade CSA
  - In these instances, radiographic features of tumors should be correlated with histology
- In difficult cases, open biopsy should target interface between tumor and normal bone
  - Best area to identify infiltrative growth pattern that is diagnostic of CSA
- In tubular bones, this distinction is not crucial as both enchondroma and low-grade CSA can be treated with thorough curettage

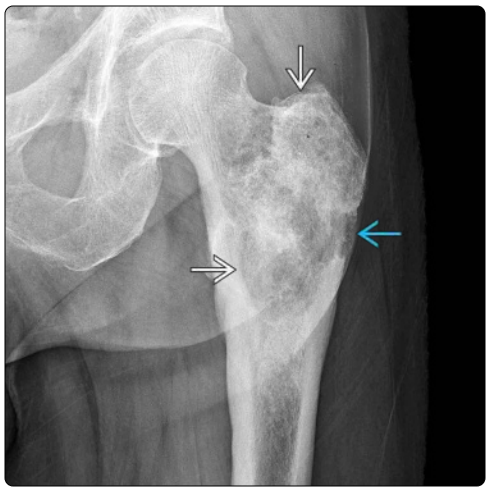
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### Mixed Lytic and Sclerotic Lesion



### Tan-Gray and Glistening Chondrosarcoma



**(Left)** *Mixed lytic and sclerotic lesion involving the left proximal femur is shown. The bone appears slightly expanded. There is some suggestion of underlying rings and arcs. No definite associated soft tissue mass is appreciated. A cortical break may be present along the lateral subtrochanteric area.* **(Right)** *Corresponding resection specimen demonstrated a tan-gray, glistening CSA filling the medullary cavity of the proximal diaphysis, greater trochanter, and base of the femoral neck.*

### Lucent Tumor With Endosteal Scalloping

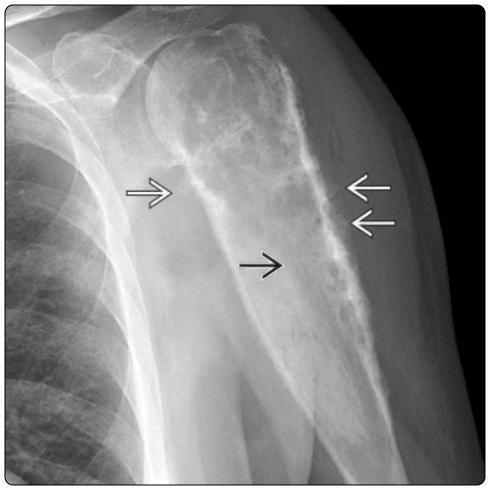


### Hyperintense Chondrosarcoma



**(Left)** *Lateral view of the distal femur shows a lucent CSA extending from the distal metaphysis to the mid shaft with several sites of endosteal scalloping and thinning of the anterior and posterior cortices.* **(Right)** *Sagittal T2-weighted MR shows replacement of the entire distal femur with a hyperintense-signal CSA. The central hypointense signal represents matrix mineralization. Endosteal scalloping and involvement of the cortices are present.*

### Lytic Chondrosarcoma



### Soft Tissue Extension



**(Left)** *AP view of the proximal humerus shows a lytic CSA involving the head, neck, and proximal shaft, which has been expanded. The distal margin is ill defined. There are scattered areas of cortical penetration and sunburst periosteal new bone along the medial and lateral cortices.* **(Right)** *Coronal T1-weighted MR shows a CSA with heterogeneous signal intensity replacing the proximal humerus with cortical disruption and soft tissue extension medially and laterally.*



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**Cortical Erosion and Soft Tissue Mass**

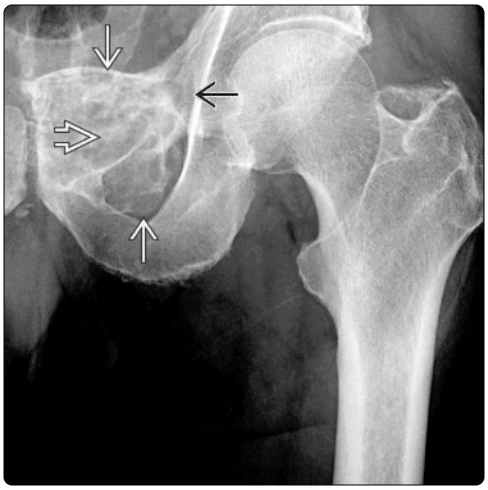


**Chondrosarcoma, Myxoid Type**



**(Left)** *Sagittal T2-weighted MR shows a CSA with hyperintense signal filling the proximal humerus. There is cortical disruption with extension into the soft tissues and edema of the deltoid.* **(Right)** *Myxoid CSA of the humerus fills the medullary cavity from the mid diaphysis to the subchondral bone plate. The solid, gray-tan-white, and hemorrhagic tumor has a lobular architecture, has expanded the diaphysis, and has eroded the medial cortex forming a soft tissue mass.*

**Lytic With Scattered Calcifications**

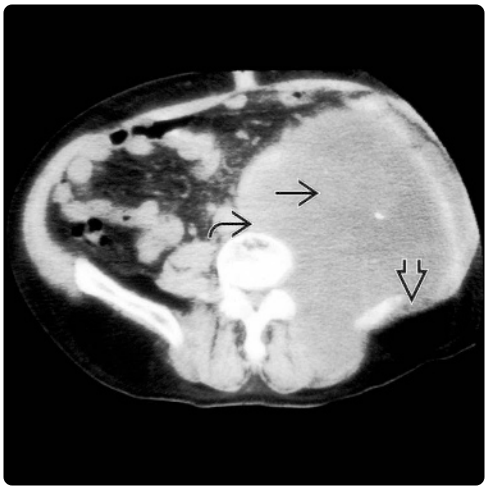


**Low Density With Large Soft Tissue Mass**

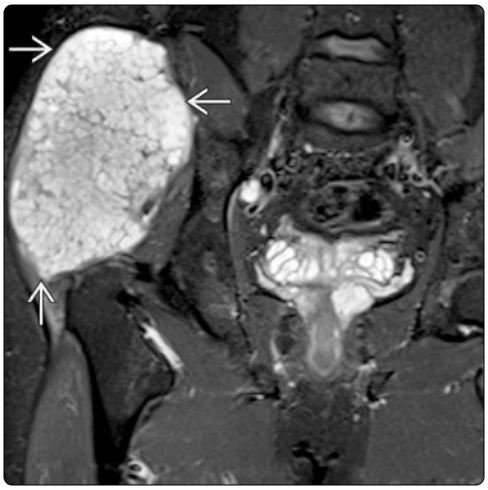


**(Left)** *AP view of the left hemipelvis shows a CSA that has expanded the left superior pubic ramus. The tumor is lytic with scattered internal irregular calcifications. The lateral margin is poorly defined and not well visualized.* **(Right)** *Coronal reformatted CT shows a large, low-density CSA that has a large soft tissue component that contains internal amorphous calcifications. The sclerosis of the medial pubis is caused by reactive bone formation.*

**Very Large Pelvic Chondrosarcoma**



**Very Large Pelvic Chondrosarcoma**

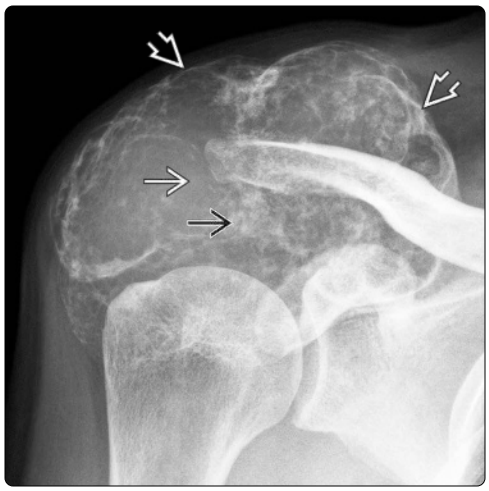


**(Left)** *Axial CT of the pelvis shows a gigantic CSA of the ilium, which has destroyed the bone and formed a large intraabdominal mass that has soft tissue density. The tumor has grown over the anterior aspect of the vertebral body.* **(Right)** *Coronal T2-weighted MR reveals a high-intensity mass that represents a hyaline-type conventional CSA. The solid tumor has a prominent nodular architecture and has destroyed the underlying ilium. It extends to the superior acetabulum rim.*

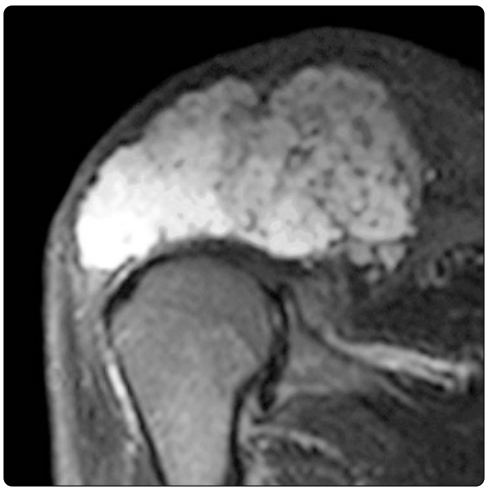


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### Destructive Tumor of Acromion



### Large Acromion Tumor

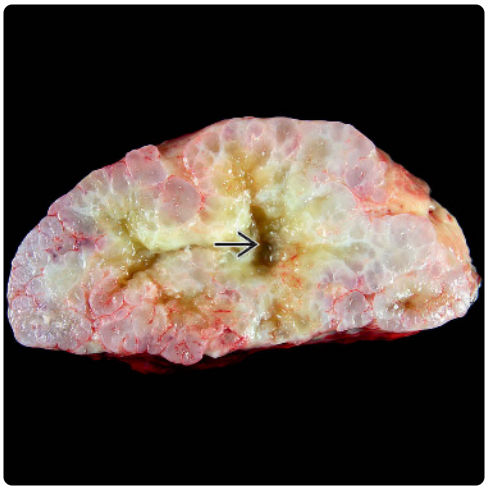


**(Left)** *A large CSA of the acromion has destroyed the bone and is confined by a thin layer of reactive bone. The tumor has a lobulated configuration corresponding to nodules of tumor. The tumor is lytic with scattered matrix densities that have a typical ring and broken ring appearance.* **(Right)** *Coronal T2-weighted MR shows the hyperintense signal of a CSA that has a bunch of grapes appearance in the acromion. The original bone has been destroyed.*

### Large Surface Chondrosarcoma



### Lobulated, Gray-Glistening Tumor

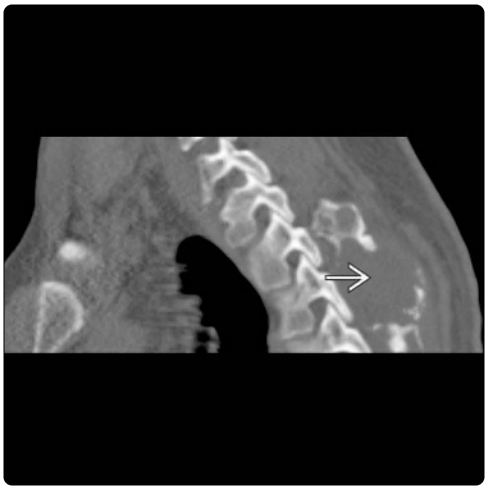


**(Left)** *A large lobulated conventional CSA has arisen on the posterior surface of the distal femur. The tumor is lytic with internal calcific radiodensities that also extend along the margin of the mass. The posterior cortex is ragged.* **(Right)** *A juxtacortical CSA has been dissected from the surface of the bone revealing a well-circumscribed mass composed of lobules of blue-gray-tan hyaline cartilage. The large tumor has areas of central cystic degeneration.*

### Chondrosarcoma of Spinous Process



### Lytic Chondrosarcoma of Spinous Process

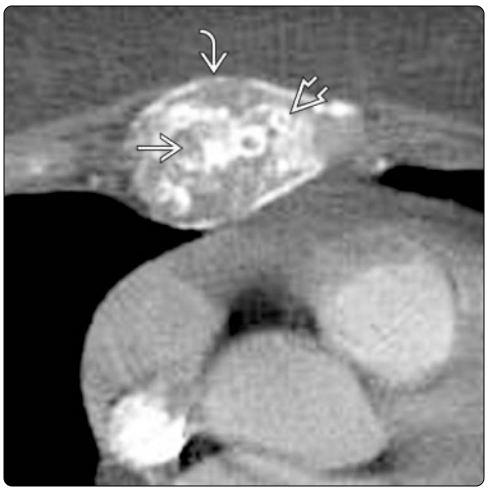


**(Left)** *Axial CT demonstrates a CSA that expands the spinous process in the upper thoracic spine. The lytic tumor is confined by reactive bone but focally penetrates it, forming a small soft tissue component with calcifications in the posterior right side.* **(Right)** *Sagittal reformatted CT scan shows a lytic expansile CSA involving the spinous process in the upper thoracic spine. There is lobulation of the posterior and inferior cortex. No internal matrix is visible.*

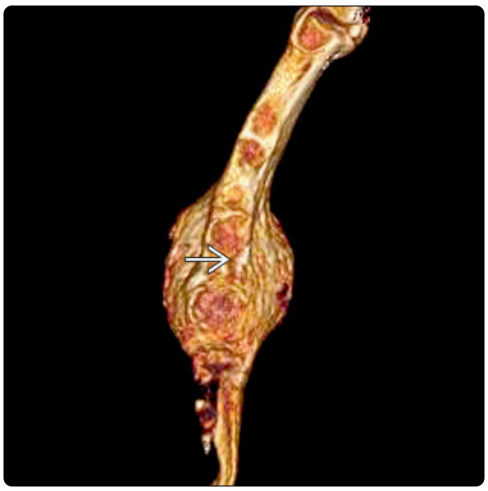


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### Mineralized Chondrosarcoma of Sternum

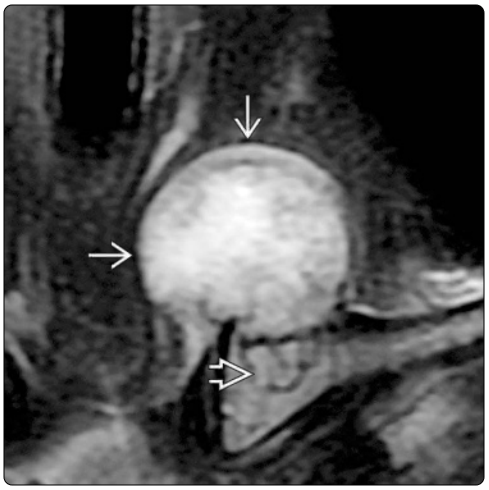


### Chondrosarcoma of Sternum



**(Left)** *Axial CT scan shows a CSA that has expanded the body of the sternum. The tumor is lytic with scattered mineralized arcs and rings typical of a hyaline cartilage tumor. The new cortex is composed of reactive bone and is focally eroded.* **(Right)** *Sagittal 3D reformatted CT scan shows a CSA arising in the inferior portion of the body of the sternum. The tumor has significantly expanded the bone, destroyed the original cortex, and bulges into the soft tissues.*

### Bright Surface Chondrosarcoma of Clavicle



### Gray-Glistening Surface Chondrosarcoma



**(Left)** *Coronal T2-weighted MR shows a conventional CSA arising on the surface of the medial clavicle that invades into the medullary canal.* **(Right)** *A juxtacortical CSA arising from the surface of the medial aspect of the clavicle is well delineated and composed of hyaline cartilage with degenerative cystic change of the central region. At the base of the mass is a triangular-shaped area of reactive bone. Note that the tumor has invaded into the medullary cavity.*

### Lytic Chondrosarcoma of Distal Phalanx



### Large Destructive Mass



**(Left)** *The distal phalanx is expanded by a lytic CSA that fills most of the bone. The proximal portion of the tumor has expanded the bone and destroyed the cortex. Arch and rings are present.* **(Right)** *A large, round CSA of the proximal phalanx of the 4th finger has destroyed the underlying bone. The tumor is lytic and contains septa representing reactive bone. Much of the tumor is surrounded by a thin rim of new subperiosteal bone.*



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**Chondrosarcoma of Hand**

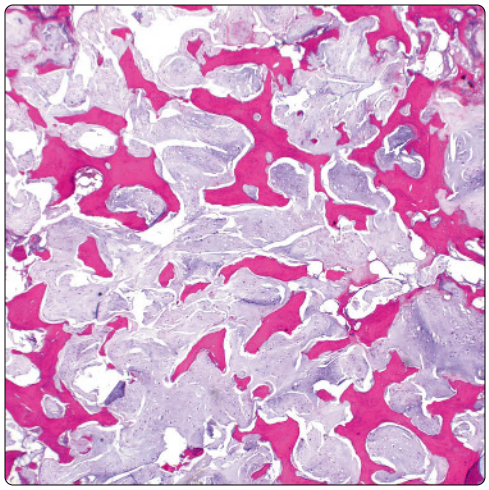


**Chondrosarcoma of Hand**

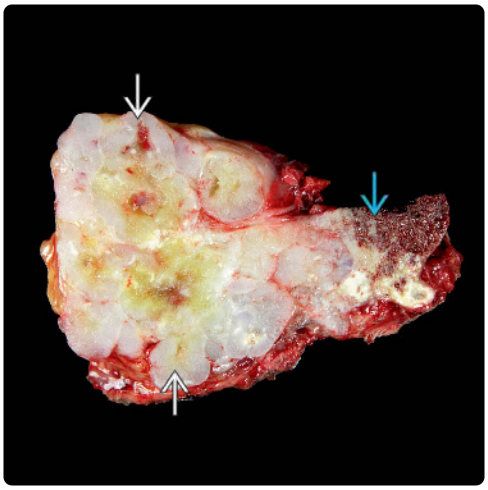


**(Left)** *Recurrent cartilaginous tumor of the proximal phalanx is shown. The tumor is lytic with vague mineralizations and appears to scallop the cortex of the bone. No obvious features of malignancy are seen on this plain radiograph.* **(Right)** *The corresponding CT scan demonstrates the tumor better. It contains some areas of mineralizations and focally has broken through the cortex and extended into the soft tissue.*

**Infiltrative Growth Pattern**

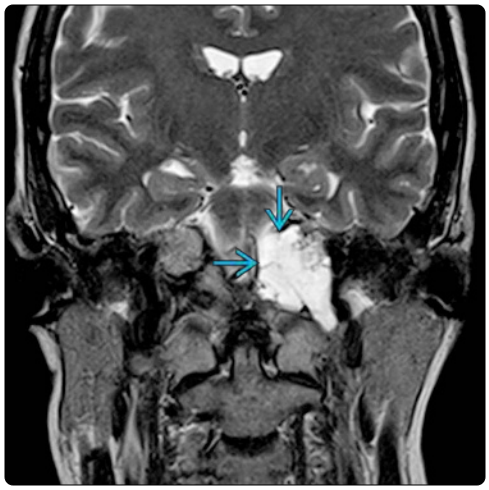


**Enchondromatosis and Chondrosarcoma**

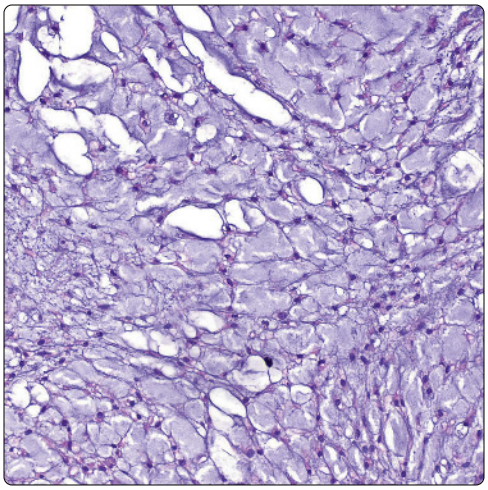


**(Left)** *Corresponding histologic features of the CSA of the proximal phalanx of the hand shows the typical infiltrative growth pattern with tumor replacing the marrow and encasing preexisting trabecular bone.* **(Right)** *CSA arising in a patient with enchondromatosis (Ollier disease) is shown. The CSA is gray-glistening and lobulated. Several small enchondromas are seen in the adjacent "normal" bone.*

**Skull Base Chondrosarcoma**



**Chondrosarcoma, Myxoid Type**

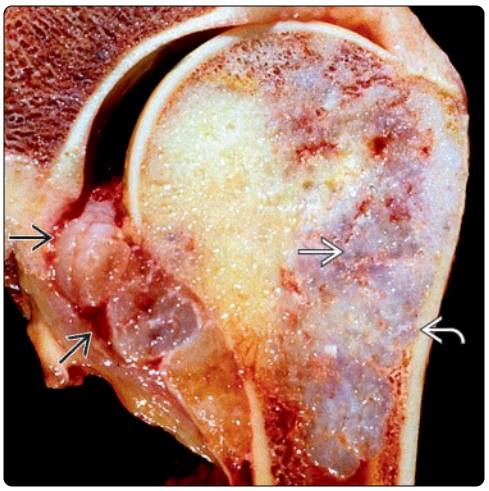


**(Left)** *CSA arising in the skull base is shown. The most common primary tumors in that location are chordoma and CSA; the latter arising in bones formed by endochondral ossification. The CSA is usually more lateral in location, like in this case, and bright on T2-weighted MR.* **(Right)** *Myxoid CSA is composed of spindle and stellate cells that float in a mucinous matrix. The tumor cells are arranged end-to-end and form necklace-like structures. The tumors have round nuclei that are hyperchromatic.*

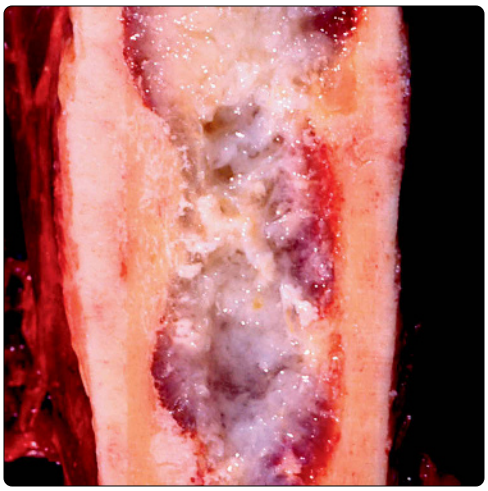


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### Extension Into Joint Space

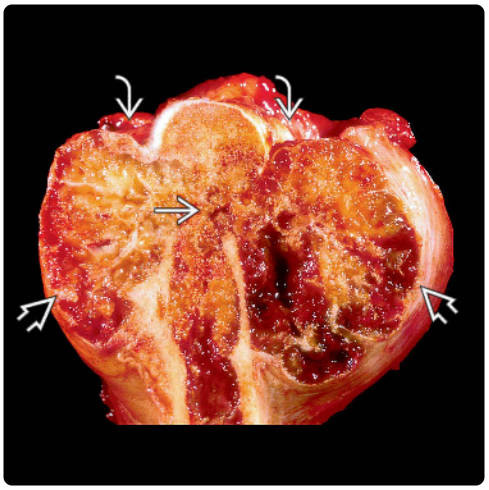


### Scalloped and Thickened Cortex



**(Left)** *Conventional hyaline-type CSA fills the humeral head, transgresses the cortex, and extends into the shoulder joint. The tumor is composed of coalescing nodules of blue-gray cartilage. Some of the nodules scallop the endosteal surface of the adjacent cortex.* **(Right)** *Myxoid and hyaline-type CSA of the femur fills the medullary cavity. The tumor is composed of friable, gray-white-tan tissue that has infiltrated the cortex resulting in its thickening.*

### Large Myxoid Chondrosarcoma

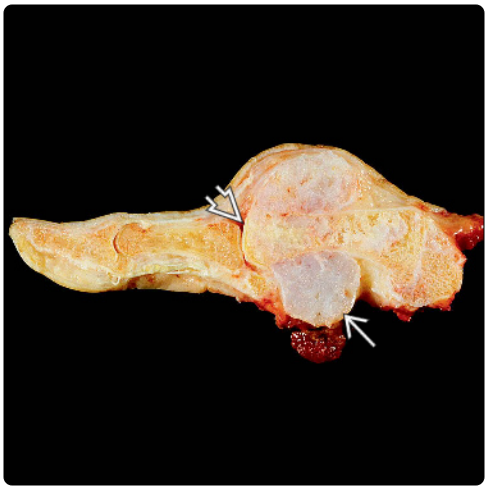


### Pathologic Fracture

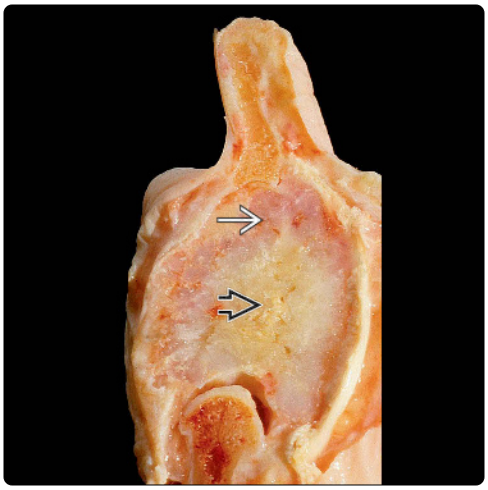


**(Left)** *A very large myxoid CSA has dramatically distorted the proximal humerus. The tumor fills and expands the medullary cavity and has destroyed the cortex, forming large medial and lateral soft tissue components. The synovium of the shoulder joint is uninvolved.* **(Right)** *A CSA involves the proximal fibula and has undergone pathologic fracture with blood filling the fracture line. The blue-gray tumor has expanded the bone and extends into the soft tissues.*

### Small Bone Chondrosarcoma



### Destructive Chondrosarcoma of Phalanx

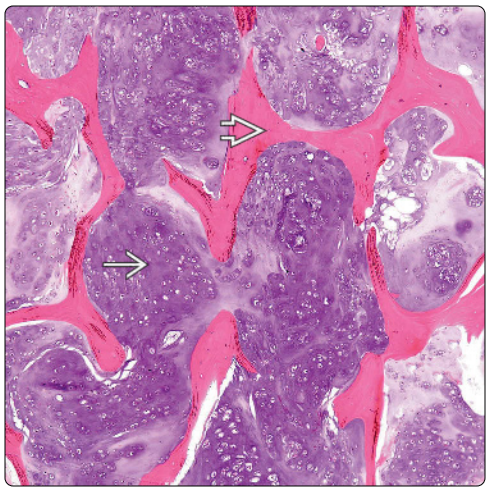


**(Left)** *A hyaline-type CSA originated in the proximal phalanx and protrudes into the soft tissues with pushing margins. The blue-tan-white tumor is solid and has significantly distorted the bone. The interphalangeal joint is intact and not involved by tumor.* **(Right)** *A conventional CSA arises in the middle phalanx and has destroyed the underlying bone. The pale blue-white tumor is undergoing degenerative myxoid change in its center. The adjacent joints are not involved.*

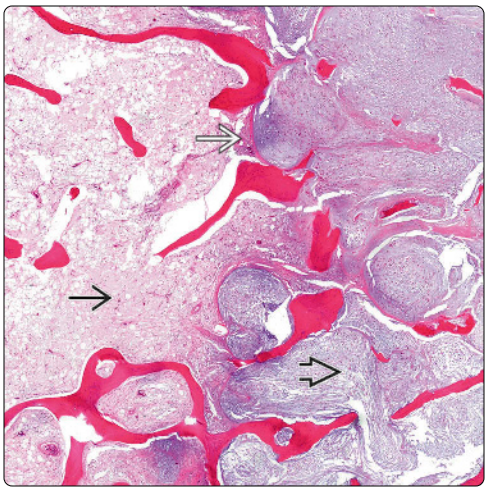


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### Infiltrating Low-Grade Chondrosarcoma

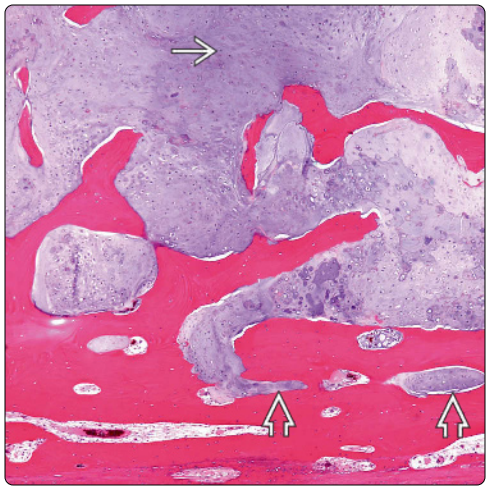


### Marrow Permeation

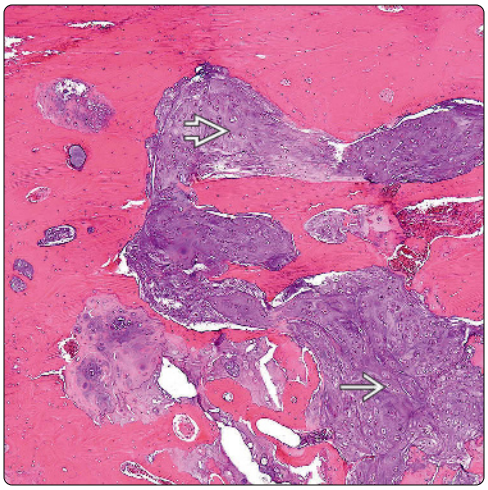


**(Left)** *Conventional hyaline CSA replaces the marrow and encases the preexisting cancellous bone. The tumor is relatively hypocellular and the matrix is basophilic and prominent, which are features typical of a grade 1 tumor.* **(Right)** *Advancing edge of a grade 2 CSA shows the interface with the uninvolved marrow, which is replaced by fibrous tissue. The tumor permeates the marrow and surrounds preexisting cancellous bone. Note the hypercellularity of the mass.*

### Tumor Permeating Haversian Systems

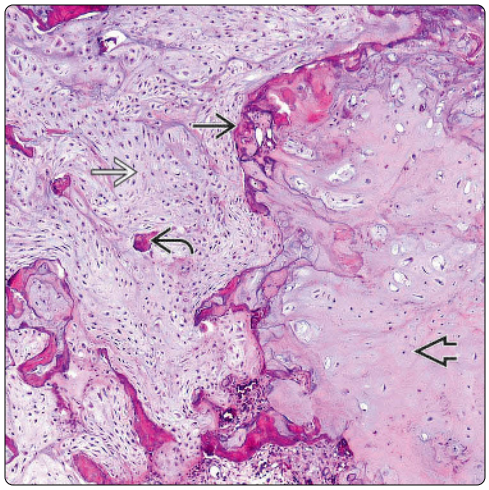


### Extensive Cortical Bone Invasion

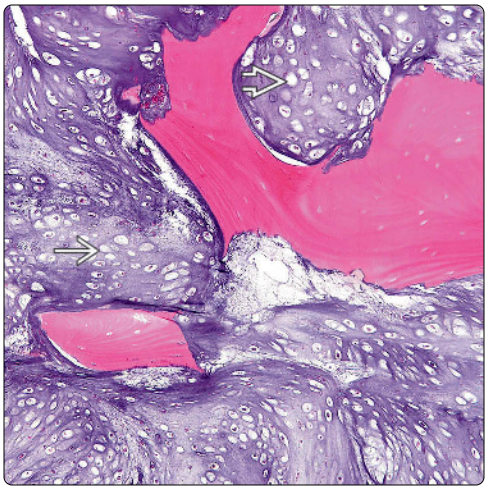


**(Left)** *Grade 1 hyaline CSA fills the medullary cavity, surrounds the bony trabeculae, and extends into the cortex. Cortical invasion is manifested by tumor permeating haversian systems, stimulating osteoclasts that cause expansion of their diameters.* **(Right)** *Grade 1 hyaline CSA demonstrates extensive invasion of the cortex. The tumor infiltrates and expands haversian canals. This mechanism is how the tumor can breach the periosteum and extend into the soft tissue.*

### Chondrosarcoma With Enchondroma



### Encasing Trabecular Bone

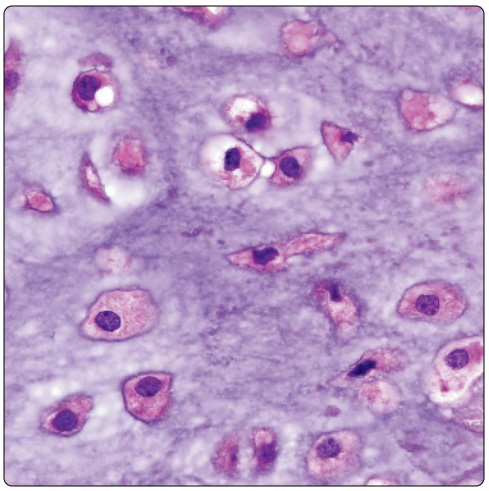


**(Left)** *A grade 2 CSA arises in association with a preexisting enchondroma. The CSA is more cellular and grows with an infiltrative pattern surrounding bony trabeculae. The enchondroma is confined by a rim of reactive bone.* **(Right)** *A grade 1 CSA replaces the fatty marrow and encompasses preexisting bony trabeculae. The tumor is not very cellular, and the chondrocytes do not show significant cytologic atypia. The lacunar spaces are prominent.*

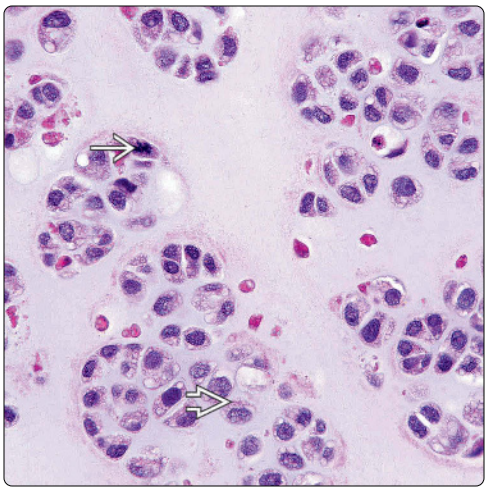


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### Grade 1 Chondrosarcoma

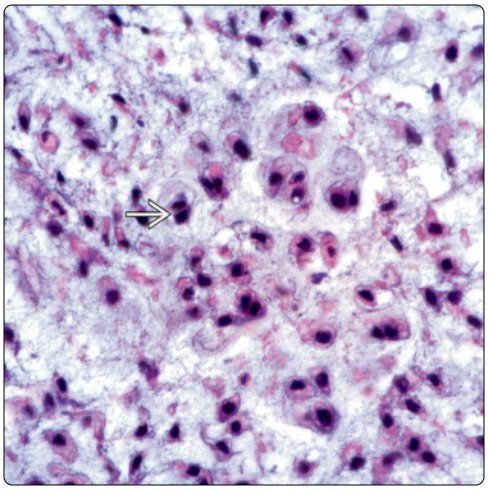


### Grade 2 Chondrosarcoma

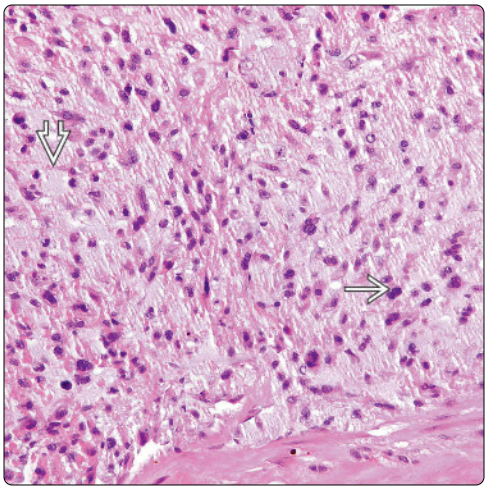


**(Left)** *Grade 1 CSA is more cellular than articular cartilage and may have the same degree or increased cellularity in comparison to enchondroma. The cells have moderate amounts of eosinophilic cytoplasm, and the nuclei have fine chromatin and small nucleoli.* **(Right)** *Grade 2 hyaline CSA is comparatively hypercellular and contains groups of neoplastic chondrocytes. The tumor cells have enlarged hyperchromatic nuclei and diminished amounts of eosinophilic cytoplasm that may be vacuolated.*

### Grade 2 Chondrosarcoma

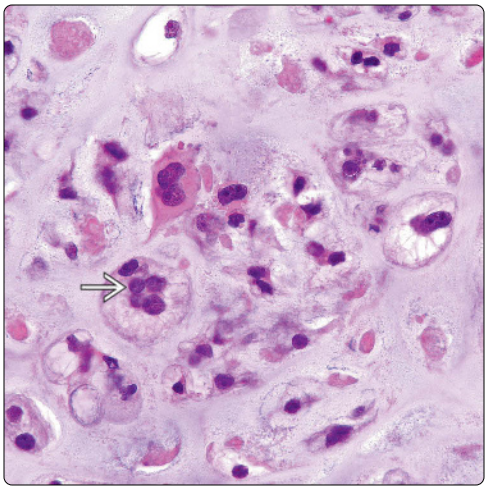


### Grade 2 Myxoid Chondrosarcoma

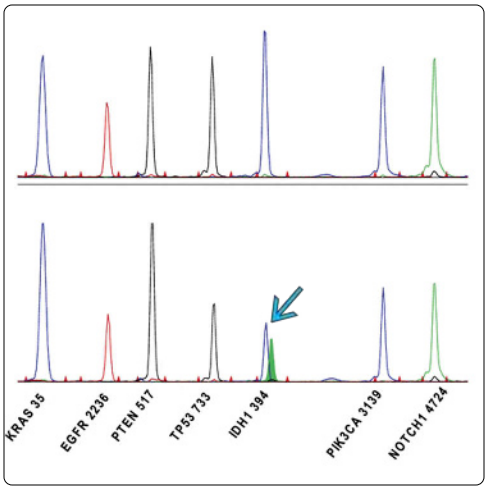


**(Left)** *Grade 2 hyaline and myxoid CSA contains round, spindle- and stellate-shaped tumor cells enmeshed in a flocculent basophilic matrix. The hypercellular tumor contains cells with enlarged, hyperchromatic nuclei and binucleate cells.* **(Right)** *Grade 2 myxoid CSA contains a bubbly mucinous matrix with spindle and stellate neoplastic chondrocytes. The tumor cells have eosinophilic cytoplasm and elongate hyperchromatic nuclei. The cytoplasmic extensions of the tumor cells come in contact with one another.*

### Grade 3 Chondrosarcoma



### *IHD1*/*IDH2* Mutational Analysis




**(Left)** *Grade 3 hyaline CSA is hypercellular and contains large neoplastic chondrocytes. The pleomorphic tumor cells contain many nuclei, which are enlarged and hyperchromatic.* **(Right)** *IDH1/IDH2 mutational analysis can sometimes be used to confirm the diagnosis of a CSA, especially distinguishing it from chondroblastic osteosarcoma. This CSA sample demonstrates an R132C IDH1 mutation (c.394 C> T), confirming the diagnosis.*



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# Dedifferentiated Chondrosarcoma

KEY FACTS

## TERMINOLOGY

- High-grade malignant neoplasm composed of 2 components
  - Well-differentiated cartilaginous tumor, usually low-grade conventional chondrosarcoma
  - Less frequently enchondroma or osteochondroma
- Component of high-grade sarcoma

## CLINICAL ISSUES

- Diagnosed in adult patients, 50-70 years old
- Develops in pelvis, femur, or humerus
- Pain
- Swelling
- Pathologic fractures
- Most patients die within 2 years of diagnosis
- Requires wide excision and systemic therapy

## IMAGING

- Low-grade element manifests as mineralized area with rings and arcs
- High-grade component has features of aggressive lytic lesion

## MACROSCOPIC

- Glistening nodules of cartilage
- Adjacent to or surrounded by pink-tan, fleshy tissue

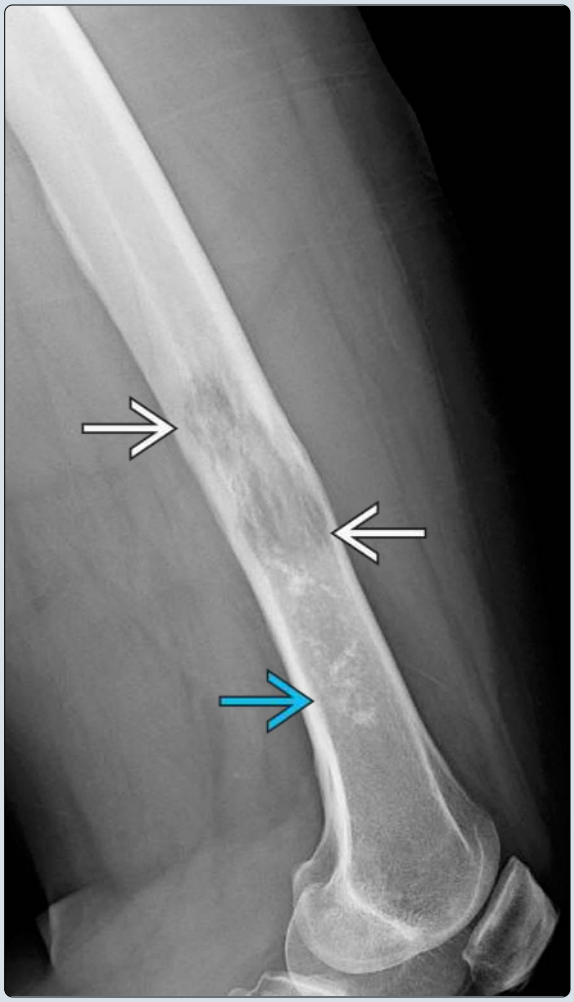
## MICROSCOPIC

- Chondroid component well differentiated
- Usually has features of cellular enchondroma or low-grade conventional chondrosarcoma
- Features of dedifferentiated component reflects its phenotype

## TOP DIFFERENTIAL DIAGNOSES

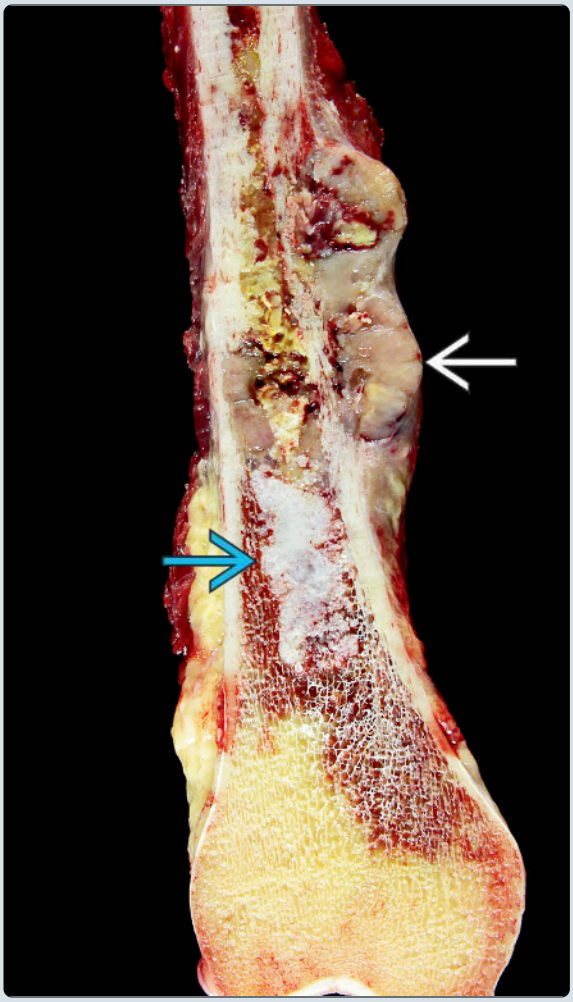
- Chondroblastic osteosarcoma, spindle cell sarcoma, metastatic sarcomatoid carcinoma

**Permeative Growth Pattern**



*Dedifferentiated chondrosarcoma of the femur is shown. The cartilaginous component contains faint rings and arches classic for low-grade cartilaginous neoplasm ⇨. Proximally, there is a lytic and permeative lesion ➡ that represents the high-grade component.*

**Dedifferentiated Chondrosarcoma**



*Corresponding resection specimen shows the gray-glistening cartilaginous component ⇨ distally. Proximally, the tumor is fleshy with yellow areas of necrosis and has broken through the cortex forming a soft tissue mass ➡.*



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## TERMINOLOGY

### Synonyms

- Chondrosarcoma with secondary mesenchymal component

### Definitions

- High-grade sarcoma arising in association with low-grade cartilaginous neoplasm with abrupt transition between 2 components
  - Cartilaginous component is usually low-grade conventional chondrosarcoma but can be enchondroma or osteochondroma

## ETIOLOGY/PATHOGENESIS

### Developmental Anomaly

- Presence of identical somatic mutations and p53 overexpression in both components suggests that they originate from single progenitor cell
- *IDH1* and *IDH2* genetic mutations have been identified in majority of chondrosarcomas

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Dedifferentiation occurs in ~ 10% of conventional chondrosarcomas; rarely seen in osteochondroma or enchondroma
- Age
  - Usually diagnosed in adult patients, 50-70 years old
- Sex
  - Males affected more frequently than females

### Site

- Pelvis, femur, or humerus

### Presentation

- Pain, swelling, pathologic fracture

### Treatment

- Wide excision and systemic therapy, although latter seems to be relatively ineffective

### Prognosis

- Very poor: Most patients die within 2 years of diagnosis

## IMAGING

### Radiographic Findings

- Low-grade element manifests as mineralized area with rings and arcs similarly to low-grade cartilaginous neoplasms; high-grade component is lytic and aggressive, showing permeation and destruction of underlying bone

### MR Findings

- May show bimorphic pattern with areas typical in appearance of low-grade chondrosarcoma and higher grade component demonstrating bone destruction

### CT Findings

- Demonstrate variably calcified tumor (low-grade chondrosarcoma) and more destructive lytic component corresponding to dedifferentiated component

## MACROSCOPIC

### General Features

- Gray glistening nodules of cartilage adjacent to or surrounded by pink-tan, fleshy tissue
- Chondroid areas can be very small and not grossly identifiable; sometimes only identified by thorough microscopic examination

## MICROSCOPIC

### Histologic Features

- Chondroid component well differentiated; usually has features of low-grade conventional chondrosarcoma or enchondroma
- High-grade sarcoma usually pleomorphic undifferentiated sarcoma
  - Variety of other phenotypes may be encountered, such as osteosarcoma, fibrosarcoma, rhabdomyosarcoma, or leiomyosarcoma

## ANCILLARY TESTS

### Immunohistochemistry

- Features of dedifferentiated component reflect its phenotype; occasionally, dedifferentiated pleomorphic spindle cell areas may express keratin

## DIFFERENTIAL DIAGNOSIS

### Chondroblastic Osteosarcoma

- Can be especially difficult when dedifferentiated component is high-grade osteosarcoma; patients with dedifferentiated chondrosarcoma are usually much older than patients with chondroblastic osteosarcoma
- Cartilaginous component in chondroblastic osteosarcoma is high grade in contrast to low-grade cartilaginous component seen in dedifferentiated chondrosarcoma

### High-Grade Spindle Cell Sarcoma

- Can be impossible to make diagnosis of dedifferentiated chondrosarcoma on small biopsy if only dedifferentiated component is sampled
- Any high-grade spindle cell sarcoma of bone in older individuals should be sampled carefully to exclude possibility of dedifferentiated chondrosarcoma

### Metastatic Sarcomatoid Carcinoma

- High-grade sarcomatoid component in dedifferentiated chondrosarcoma can be strongly keratin positive making it difficult to distinguish from carcinoma
- Careful sampling and review of radiographic images can help in identifying underlying low-grade cartilaginous component

## SELECTED REFERENCES

1. Kerr DA et al: Molecular distinction of chondrosarcoma from chondroblastic osteosarcoma through IDH1/2 mutations. Am J Surg Pathol. 37(6):787-95, 2013

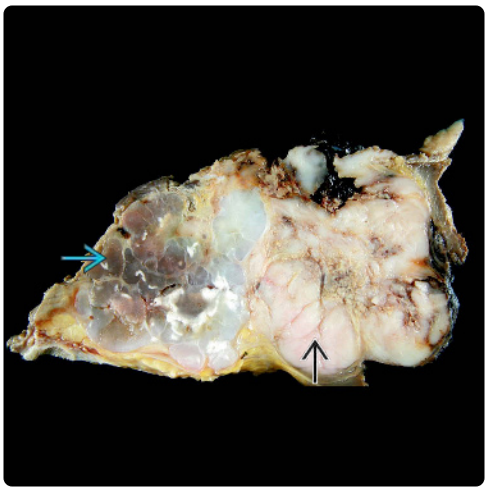


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**Pelvis**

**Fleshy, High-Grade Sarcoma**



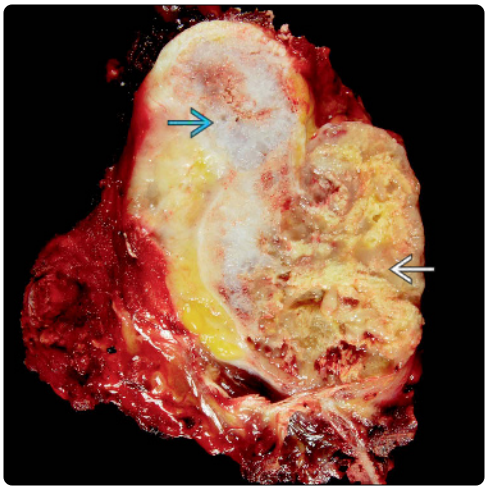


**(Left)** *Axial CT of a dedifferentiated chondrosarcoma of the pelvis shows calcifications in a pattern typical of cartilaginous neoplasms. A high-grade component lacking calcifications is also noted.* **(Right)** *Corresponding resection specimen of the pelvic dedifferentiated chondrosarcoma composed of gray-glistening cartilaginous tissue ⇨ juxtaposed to the tan, fleshy, high-grade dedifferentiated component ⇨ is shown.*

**Scapula**

**Gray-Glistening and Fleshy**

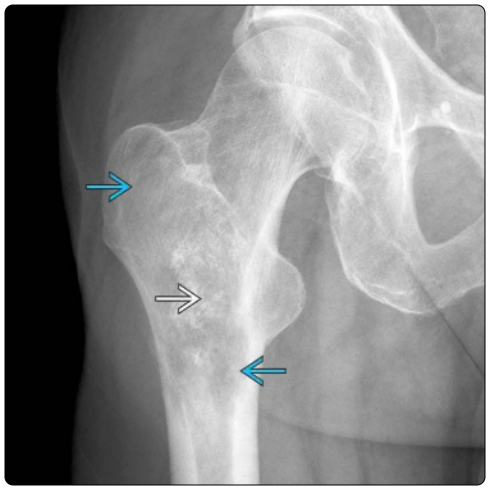




**(Left)** *Dedifferentiated chondrosarcoma arising in the scapula is shown. In this MR, the cartilaginous component is bright ⇨, whereas the high-grade dedifferentiated component is hypointense ⇨.* **(Right)** *Corresponding resection specimen of the dedifferentiated chondrosarcoma of the scapula is shown. The cartilaginous component ⇨ is gray-glistening and shows abrupt transition to a high-grade, fleshy, and necrotic sarcoma ➡.*

**Mineralized and Lucent**

**Pathologic Fracture**



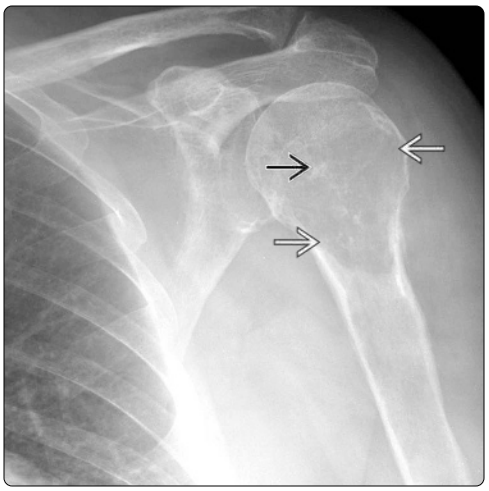


**(Left)** *AP radiograph of the right hip reveals a lesion of the femoral intertrochanteric region. It contains a component of a well-formed cartilage mineralization in the more central part of the lesion ➡. The more peripheral parts have no detectable mineralization, consistent with high-grade tumor ⇨.* **(Right)** *AP radiograph of a dedifferentiated chondrosarcoma arising in the right distal femur shows a pathological fracture ➡ through a lesion ➡ of the distal metaphysis.*

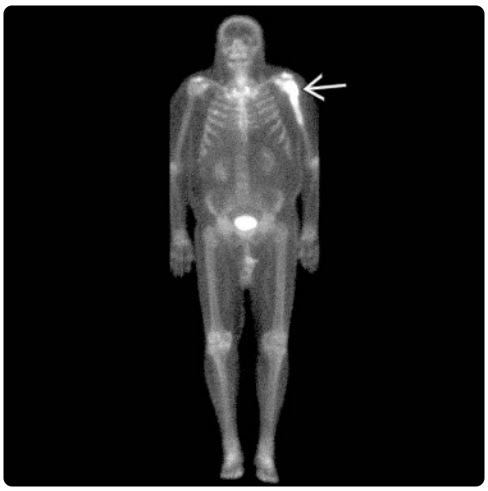


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### Predominantly Lytic Lesion



### Hot on Bone Scan

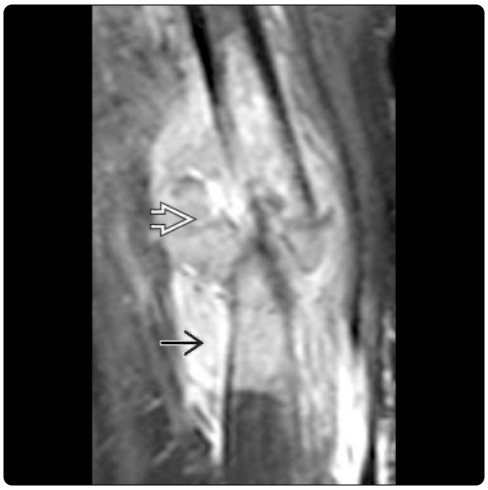


**(Left)** *AP radiograph of a dedifferentiated chondrosarcoma arising in the shoulder demonstrates a lytic lesion in the medullary cavity of the humerus. Proximally, there is very faint mineralization representing the preexisting low-grade cartilaginous tumor, which could easily be overlooked.* **(Right)** *This radioisotope bone scan of a patient with a dedifferentiated chondrosarcoma of the proximal humerus shows the extent of the intraosseous tumor.*

### Pathologic Fracture of Humerus

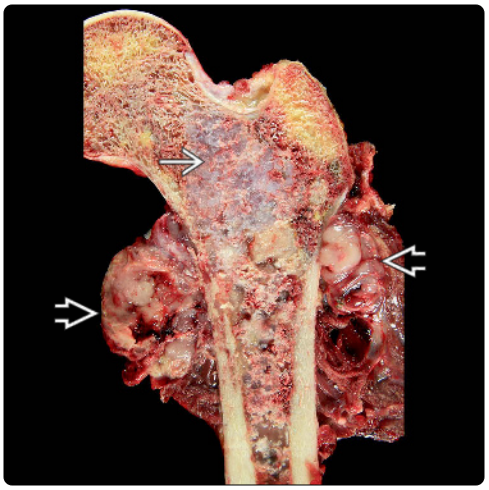


### Dedifferentiated Chondrosarcoma

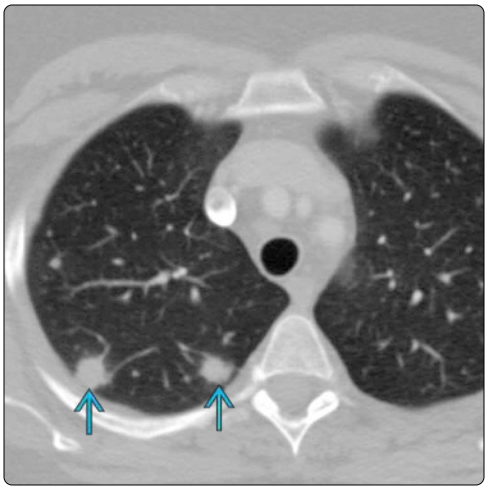


**(Left)** *In this dedifferentiated chondrosarcoma of the humerus, the ring and arc pattern of mineralized cartilage is seen centrally, representing the low-grade cartilaginous component. More peripherally, there is a lytic infiltrating tumor, consistent with the dedifferentiated component. A pathological fracture is present.* **(Right)** *T2-weighted MR of a dedifferentiated chondrosarcoma shows the tumor involving bone and soft tissue as well as a large amount of muscle edema.*

### Cartilaginous and Fleshy Component



### Pulmonary Metastases

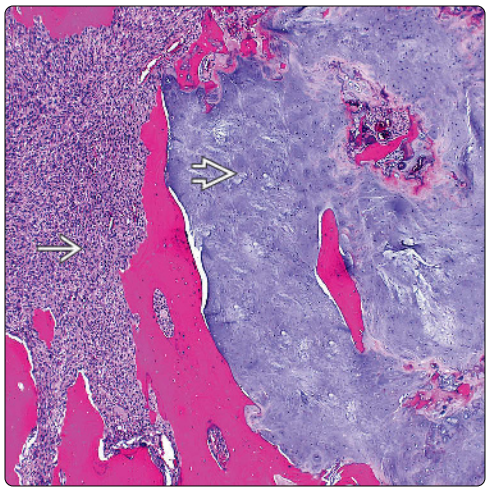


**(Left)** *Gross photograph of a dedifferentiated chondrosarcoma arising in the proximal femur is shown. The cartilaginous component is within the medullary cavity, whereas the tan, hemorrhagic, fleshy dedifferentiated component has broken through the cortex and extended into adjacent soft tissues.* **(Right)** *It is very common for patients to have pulmonary metastases at the time of diagnosis of a dedifferentiated chondrosarcoma. Several lung nodules are seen in this patient.*

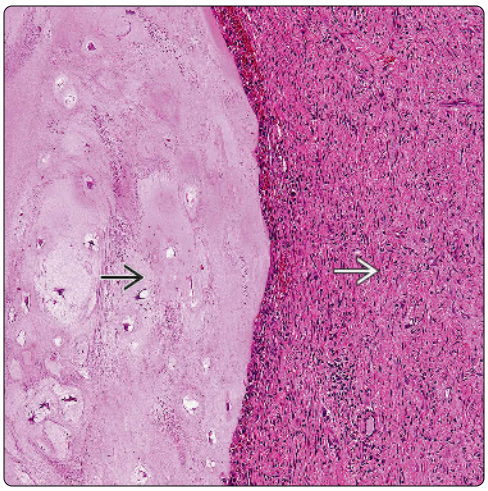


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### Infiltrative Growth Pattern

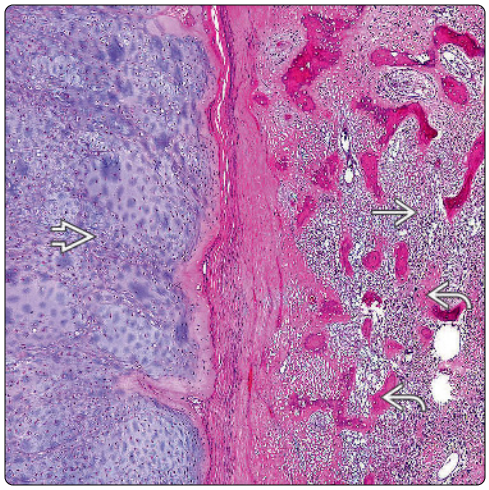


### Abrupt Transition

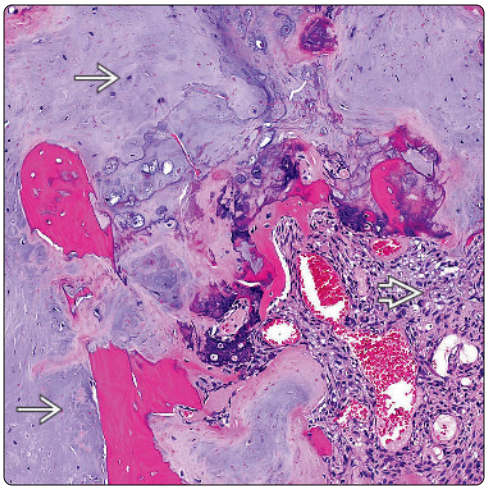


**(Left)** *In this dedifferentiated chondrosarcoma, the chondrosarcomatous component is low grade but demonstrates an infiltrative growth pattern. There is an abrupt transition to the high-grade sarcomatous component.* **(Right)** *A dedifferentiated chondrosarcoma shows abrupt transition between the low-grade chondroid component and the high-grade sarcoma, which has the appearance of an undifferentiated pleomorphic sarcoma.*

### High-Grade Osteosarcoma

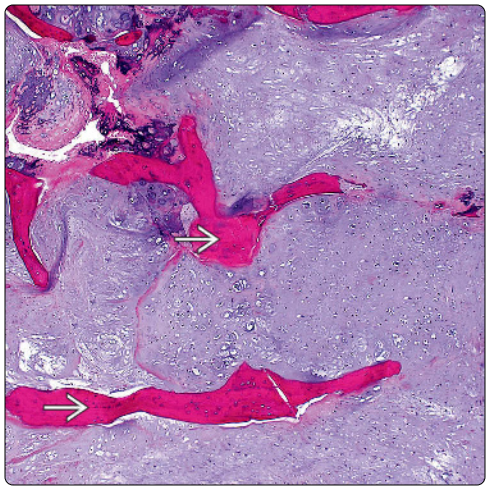


### Small Focus of Dedifferentiation

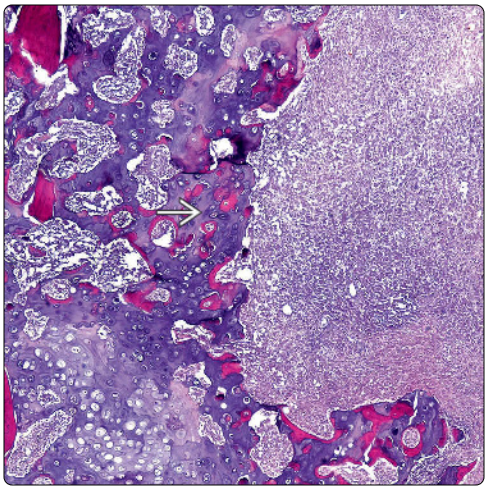


**(Left)** *A dedifferentiated chondrosarcoma with the dedifferentiated component composed of high-grade osteosarcoma is shown. The chondroid component is low grade, whereas the high-grade sarcomatous portion shows neoplastic bone formation, confirming the diagnosis of a high-grade osteosarcoma.* **(Right)** *In this curettage specimen of a dedifferentiated chondrosarcoma, the dedifferentiated component is small and can be easily overlooked. The chondroid areas are low grade.*

### Low-Grade Chondrosarcoma



### Dedifferentiated Enchondroma

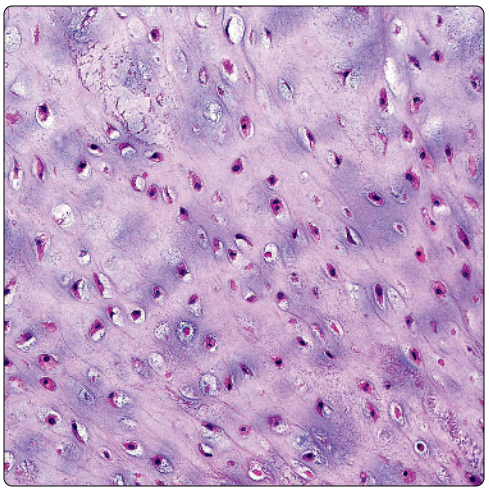


**(Left)** *The chondrosarcomatous component in this dedifferentiated chondrosarcoma is hypocellular but grows with an infiltrative growth pattern.* **(Right)** *Dedifferentiated chondrosarcoma shows abrupt transition between the cartilaginous component and the high-grade sarcoma. In this example, the cartilaginous component has the appearance of an enchondroma, demonstrating minimal atypia and lack of infiltrative growth pattern.*

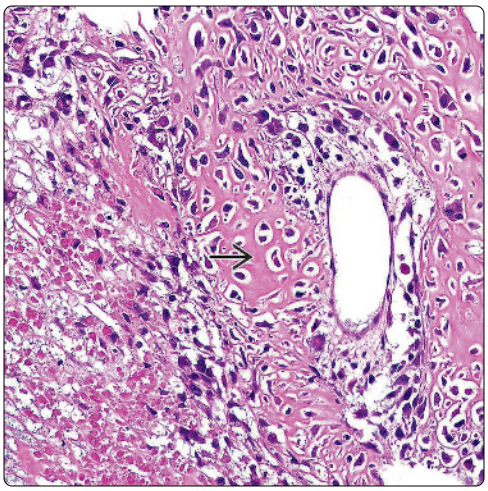


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Low-Grade Cartilaginous Component

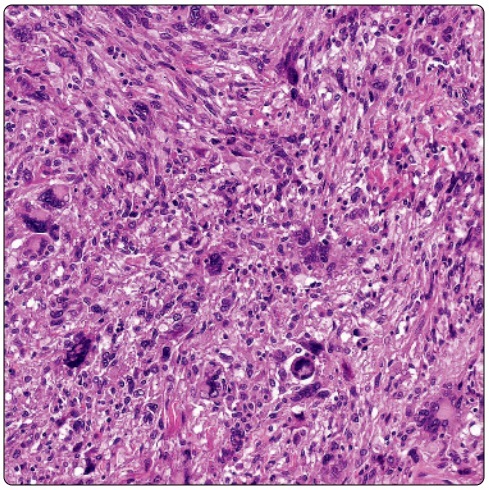


High-Grade Osteosarcoma

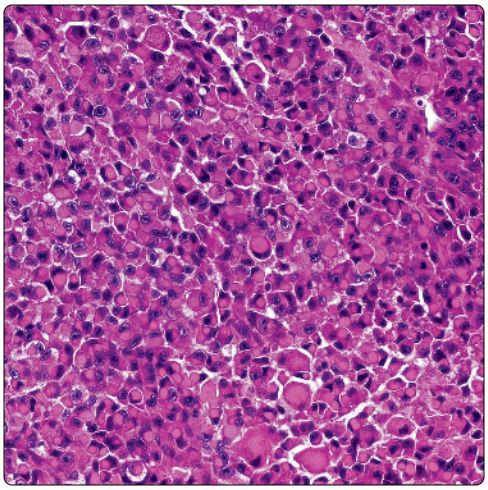


**(Left)** *The cartilaginous component in a dedifferentiated chondrosarcoma usually shows the appearance of a low-grade chondrosarcoma with minimal atypia, as seen here.* **(Right)** *High-power view shows dedifferentiated chondrosarcoma where the dedifferentiated component has the appearance of a high-grade osteosarcoma. The neoplastic cells are obviously malignant and deposit bone in a lace-like ⇨ manner as seen in conventional osteosarcoma.*

Undifferentiated Pleomorphic Sarcoma

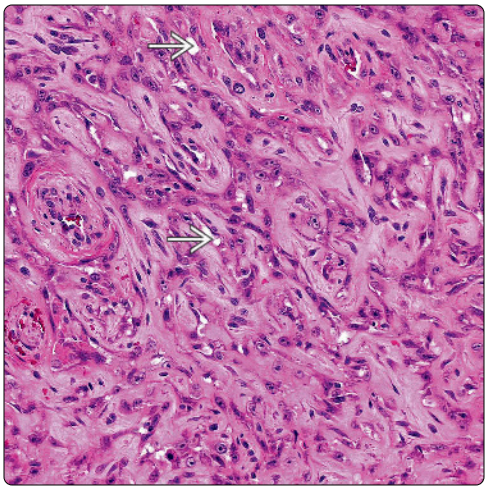


Rhabdomyosarcoma

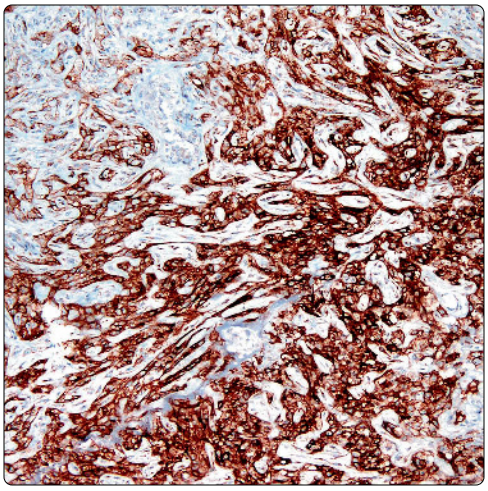


**(Left)** *A typical dedifferentiated component in a dedifferentiated chondrosarcoma shows a high-grade pleomorphic undifferentiated sarcoma. It would be impossible to make the diagnosis if the biopsy specimen contained only this component.* **(Right)** *A dedifferentiated chondrosarcoma with rhabdomyosarcoma component is shown. The rhabdomyosarcoma is composed of cells with eccentric nuclei and abundant eosinophilic cytoplasm.*

Angiosarcoma



D2-40 Immunohistochemical Stain



**(Left)** *In this dedifferentiated chondrosarcoma, the dedifferentiated portion is composed of a high-grade angiosarcoma. The high-grade angiosarcomatous component is composed of malignant endothelial cells that form slit-like vascular spaces ➡.* **(Right)** *High-grade dedifferentiated chondrosarcoma where the dedifferentiated component is composed of a high-grade angiosarcoma is shown. The endothelial cells demonstrate diffuse and strong cytoplasmic staining for D2-40 by immunohistochemistry.*



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# Clear Cell Chondrosarcoma

KEY FACTS

## TERMINOLOGY

- Low-grade chondrosarcoma (CSA) subtype

## CLINICAL ISSUES

- Uncommon; accounts for 2% of all CSAs
- Peak incidence: 3rd-4th decades of life
- Usually involves long bones, especially proximal femur and humerus
- Local recurrence rate is ~ 16% with 10% of patients eventually dying of disease
- Treated by wide resection, often curative
  - Inadequate initial treatment results in high rate of local recurrence and metastasis

## IMAGING

- Typically arises in epiphysis or apophysis
- Well defined, lytic, with punctate radiodensities
- High signal intensity on T2-weighted images

## MACROSCOPIC

- Centered in epiphysis or apophysis
- 5-10 cm in size
- Circumscribed, tan-gray, solid with hemorrhagic cysts
- May erode cortex and involve soft tissue

## MICROSCOPIC

- Lobular architecture, infiltrates marrow, encases bone
- Large tumor cells with abundant clear or pink cytoplasm
- Metaplastic bone rimmed by osteoblasts and osteoclasts
- Expresses S100 protein
- Contains small foci of conventional CSA

## TOP DIFFERENTIAL DIAGNOSES

- Chondroblastoma
- Conventional CSA
- Osteosarcoma
- Metastatic clear cell (CC) renal cell carcinoma

### Lytic Mass With Punctate Calcifications



### Well-Circumscribed Mass

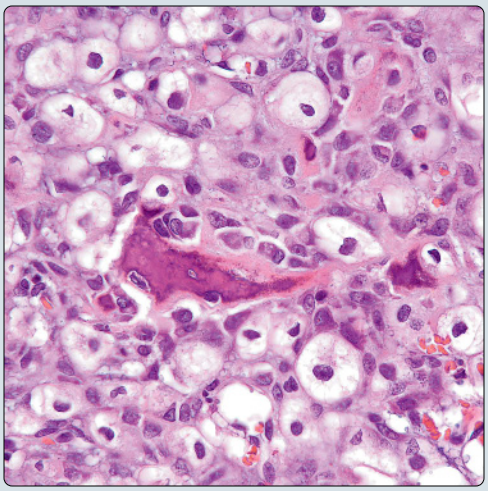


**(Left)** *AP radiograph shows a lytic subarticular lesion of the femoral head. The lesion has faint internal mineralization and is demarcated from the surrounding bone by a thin zone of reactive sclerosis.* **(Right)** *Coronal T1-weighted MR shows a clear cell chondrosarcoma (CC-CSA) of the femoral head. The tumor has low signal and is well circumscribed by a dark margins that represents sclerotic bone.*

### Hemorrhagic, Tan-Gray Tumor



### Sheets of Large Clear Cells



**(Left)** *This femoral head contains a CC-CSA that extends to the subchondral bone plate. The well-circumscribed, oval tumor is heterogeneous with gray-glistening, white, and hemorrhagic areas.* **(Right)** *CC-CSA is composed of sheets of large cells that have clear and eosinophilic cytoplasm. The tumor contains a trabeculum of metaplastic bone that is rimmed by nonneoplastic osteoblasts.*



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## TERMINOLOGY

### Abbreviations

- Clear cell chondrosarcoma (CC-CSA)

### Synonyms

- CC variant of CSA

### Definitions

- CSA variant with large chondrocytes having clear cytoplasm

## ETIOLOGY/PATHOGENESIS

### Neoplasm

- Mutation in mesenchymal stem cell producing neoplasm

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Uncommon; accounts for 2% of CSA
- Age
  - Most tumors arise during adulthood
    - Peak incidence 3rd-4th decades; rare in children and elderly
- Sex
  - Male predominance (M:F = 1.3-2:1)

### Site

- Arises in epiphysis or apophysis of long tubular bones
  - Proximal femur and humerus most common
- Other sites: Rib, vertebra, short tubular bones

### Presentation

- Local pain, often of long duration

### Treatment

- En bloc resection with negative margins
- Adjuvant radiation for incomplete resection

### Prognosis

- Behaves as low-grade CSA and may have prolonged clinical course
- Local recurrence rate depends on margin status
  - 16-20% recur, 25% metastasize; 10-year survival: 89%
- Dedifferentiated CC-CSA very aggressive

## IMAGING

### Radiographic Findings

- Oval, well-defined sclerotic margin; margin can be indistinct
- Lytic with punctate calcifications
- Expands bone with thinned or disrupted cortex
- Periosteal reaction is frequently absent

### MR Findings

- Bright on T2- and low signal on T1-images

### CT Findings

- Sharp sclerotic margins and punctate radiodensities

### Bone Scan

- Avid uptake on technetium bone scan

## MACROSCOPIC

### General Features

- Centered in epiphysis or apophysis
- Oval, well circumscribed, solid, sometimes cystic
- Soft to firm, tan-white to gray, glistening, focally gritty
- May destroy cortex and push into soft tissues

### Size

- 5-10 cm in diameter

## MICROSCOPIC

### Histologic Features

- Lobular, infiltrates marrow encasing preexisting trabeculae
- Sheets of large cells with abundant clear-pink cytoplasm
  - Cytoplasm rich in PAS(+) diastase-sensitive glycogen
- Metaplastic woven bone rimmed by osteoblasts and scattered osteoclasts
- Contains foci of low-grade hyaline-type CSA
- Aneurysmal bone cyst-like change sometimes present
- Dedifferentiation into high-grade spindle cell sarcoma rare

## ANCILLARY TESTS

### Immunohistochemistry

- Cells express S100 protein and collagen II

### Electron Microscopy

- Ultrastructurally, neoplastic cells contain abundant intracytoplasmic glycogen

### Genetics

- Lacks *IDH1* and *IDH2* mutations

## DIFFERENTIAL DIAGNOSIS

### Chondroblastoma

- Arise in epiphysis of long tubular bone
- Histologically different; cells in CC-CSA are larger, contain more clear cytoplasm, and lack nuclear grooves

### Conventional Chondrosarcoma

- Unusual to arise epiphyses
- Smaller cells and lacks metaplastic bone formation

### Osteosarcoma

- Contains neoplastic bone
- Classic type has greater atypia and mitotic activity

### Metastatic Clear Cell Renal Cell Carcinoma

- More vascular and no neoplastic cartilage

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Large CC with admixture of metaplastic bone and foci of hyaline CSA

## SELECTED REFERENCES

1. Meijer D et al: Genetic characterization of mesenchymal, clear cell, and dedifferentiated chondrosarcoma. Genes Chromosomes Cancer. 51(10):899-909, 2012
2. Bjornsson J et al: Clear cell chondrosarcoma of bone. Observations in 47 cases. Am J Surg Pathol. 8(3):223-30, 1984



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### Lytic and Blastic Mass

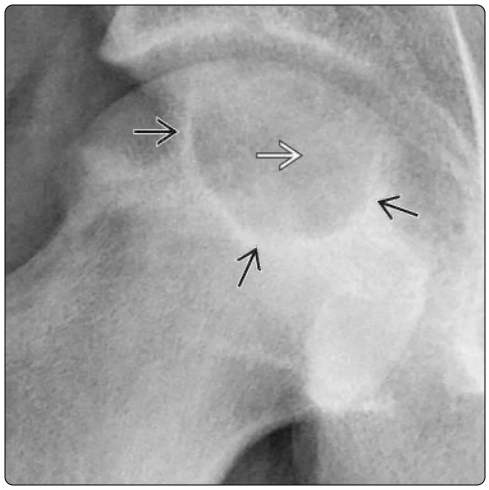


### Heterogenous Tumor

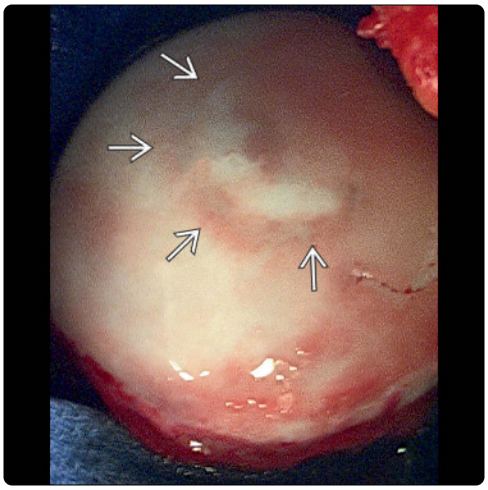


**(Left)** *The tumor involves the humeral head and presents as a mixed lytic and blastic mass ⇨. The margins vary from well circumscribed and sclerotic to poorly defined.* **(Right)** *In this coronal T2-weighted MR the CC-CSA is heterogenous in signal. Portions of the tumor have low intensity and other nodular areas have increased intensity; the latter likely consists of hyaline-type neoplastic cartilage.*

### Round Lytic Mass in Femoral Head



### Rim of Hyperemia Surrounding Tumor



**(Left)** *The tumor manifests in this radiograph as a lytic, round radiolucency ⇨. The margins are well circumscribed and sclerotic ⇨. The remainder of the femoral head is unremarkable.* **(Right)** *Surgical exposure shows the femoral head from the accompanying radiograph is being excised because it contains a CC-CSA. The tumor is located beneath the articular surface and is delineated by a rim of hyperemia ⇨.*

### Mixed Lytic and Blastic Mass



### Sclerotic and Lytic Tumor

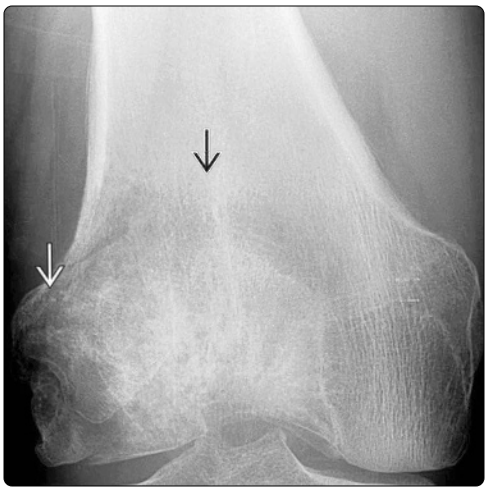


**(Left)** *The pubis is distorted by a mildly expansile lytic and blastic tumor that does not have well-defined margins. The blastic component is dense and irregular.* **(Right)** *This is the accompanying axial CT to the radiograph in the previous image. The tumor involves the body and superior ramus of the pubis and has lytic and sclerotic foci.*

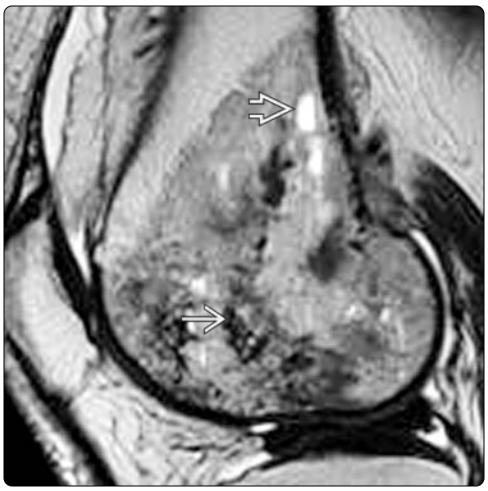


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### Large Lytic and Mineralized Mass

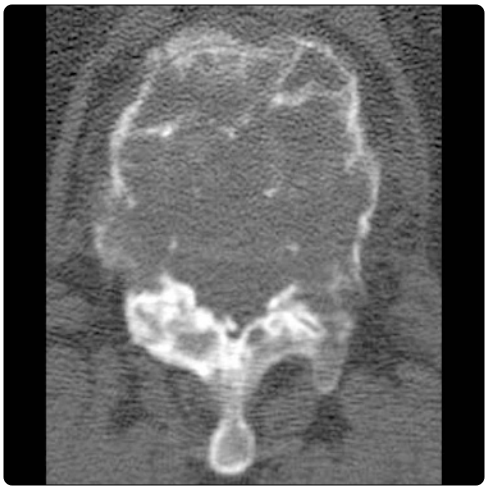


### Mass Filling Epiphysis and Metaphysis



**(Left)** *CC-CSA of the distal femur manifests as a geographic area of radiolucency and has an indistinct proximal margin ⇨. The tumor contains scattered punctate radiodensities ➡.* **(Right)** *Sagittal T2-weighted MR shows that the large tumor extends from the subchondral bone plate into the metaphysis. The tumor has intermediate signal intensity, and the low-signal regions ➡ represent areas of calcification. The bright foci are areas of cystic degeneration ➡.*

### Large Tumor Involving Vertebra



### Mass Extending Into Spinal Canal

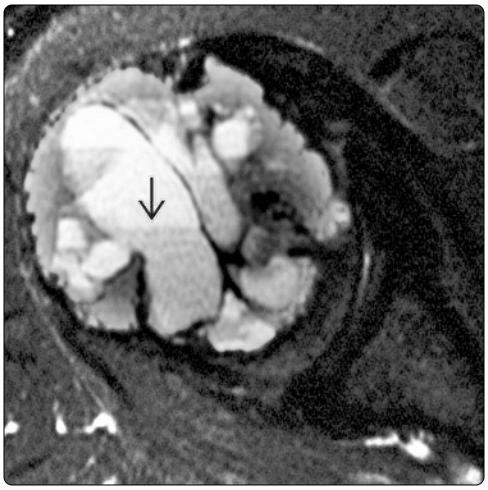


**(Left)** *CT scan shows a CC-CSA arising within a vertebral body, a very rare location. The tumor extends into both pedicles and is lytic with scattered fine calcifications. It has resulted in relatively little deformity of the bone and appears to be contained by the periosteum.* **(Right)** *T2-weighted sagittal MR shows a CC-CSA bulging into the spinal canal. Calcifications of the lesion are represented as focal dark areas ➡.*

### Expansile Lytic Mass



### Numerous Cysts With Fluid-Fluid Levels

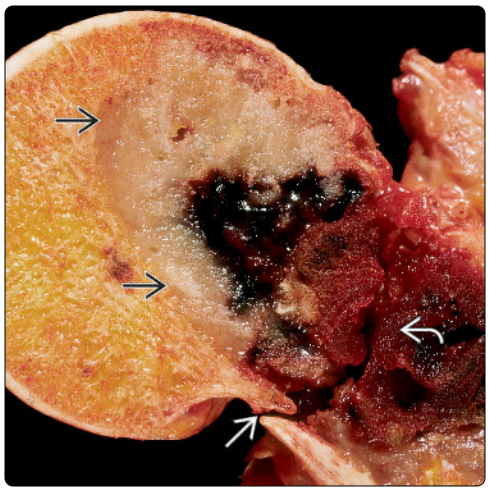


**(Left)** *AP radiograph shows an expansile lytic lesion ➡ of the distal 1st metatarsal. The lesion contains focal internal calcifications. There is collapse of the subchondral bone plate due to pathological fractures of the cancellous bone.* **(Right)** *T2-weighted MR shows a CC-CSA of the proximal humerus with solid and cystic components with fluid-fluid levels ⇨ representing secondary aneurysmal bone cyst formation.*



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**Tan, Hemorrhagic Tumor**

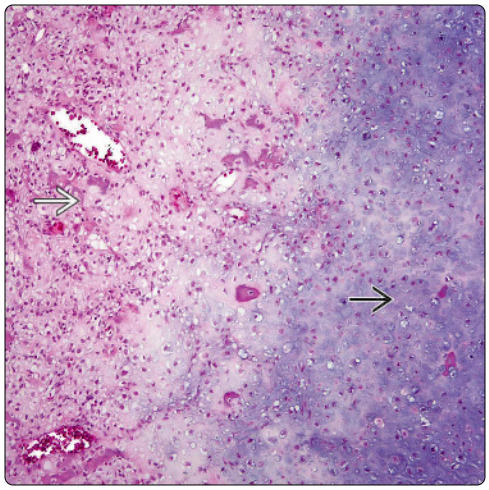


**Large Mass With Bone Cement**

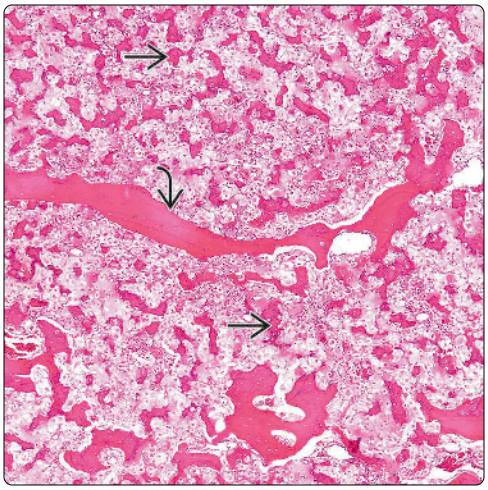


**(Left)** *CC-CSA ⇨ of the femoral head and neck that has been previously biopsied with the defect filled with hemorrhagic gel foam ⇨ is shown. The tumor is well circumscribed and is tan-gray and glistening. Note the fracture of the femoral neck ⇨.* **(Right)** *CC-CSA ⇨ of the distal femur extends from the base of the condyles into the distal diaphysis. The tumor has been previously biopsied, and the defect has been filled with bone cement ⇨. The remaining tumor is gray-red and gritty in appearance ⇨.*

**Cartilaginous Area**

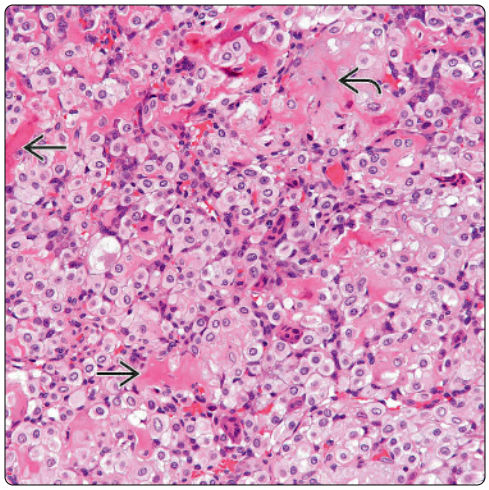


**Infiltrative Growth Pattern**

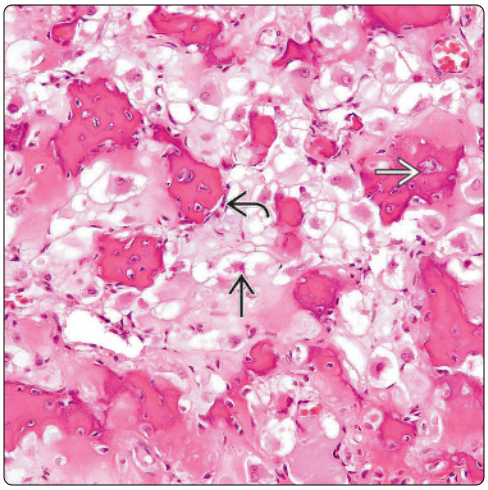


**(Left)** *CC-CSA contains regions of conventional hyaline-type CSA ⇨. The hyaline component is blue and borders the clear cell component ⇨ with a zone of transition between the 2 types.* **(Right)** *CC-CSA is seen growing with an infiltrative pattern in the medullary canal. The tumor encases the preexisting trabecular bone ⇨. The metaplastic bone ⇨ within the tumor is prominent and often causes confusion with osteosarcoma.*

**Clear Cells and Metaplastic Bone**



**Metaplastic Bone**

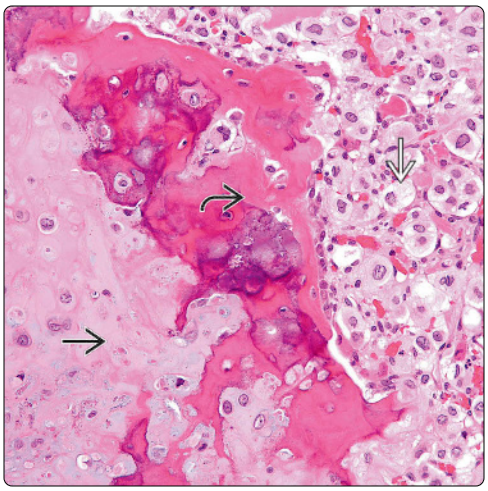


**(Left)** *CC-CSA is seen composed of sheets of large cells with pale pink cytoplasm. Trabeculae of metaplastic bone ⇨ and a small focus of neoplastic hyaline cartilage ⇨ are present.* **(Right)** *Abundant metaplastic bone ⇨ is present in CC-CSA. The neoplastic cells ⇨ surround the woven bone, which is focally lined by benign osteoblasts ⇨.*

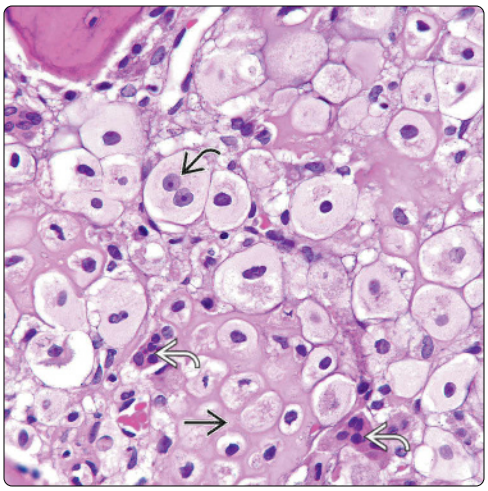


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### Metaplastic Bone and Tumor Cartilage

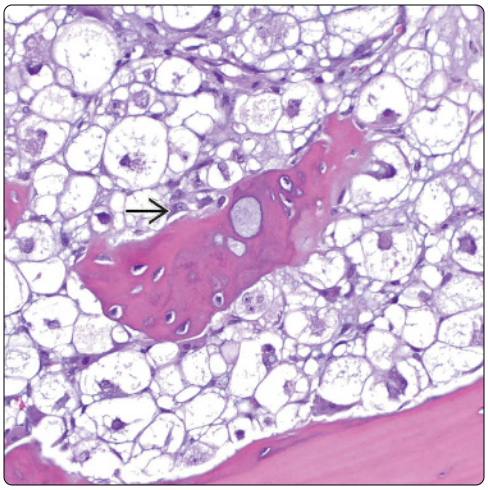


### Sheets of Clear Cells

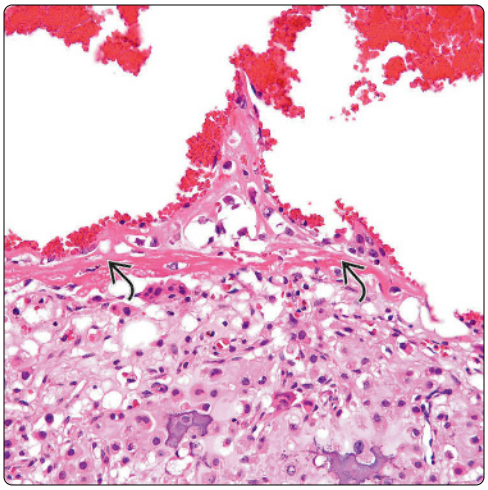


**(Left)** *A focus of conventional hyaline-type CSA is in a CC-CSA is shown. The hyaline component is undergoing enchondral ossification. The clear cell component consists of large polyhedral cells with abundant pale pink and clear cytoplasm.* **(Right)** *The neoplastic cells of CC-CSA may be binucleate and are large with abundant pale pink cytoplasm. The nuclei range from round to oval and often have conspicuous nucleoli. Note the scattered osteoclasts and small area of neoplastic hyaline matrix.*

### Large Cells With Clear Cytoplasm

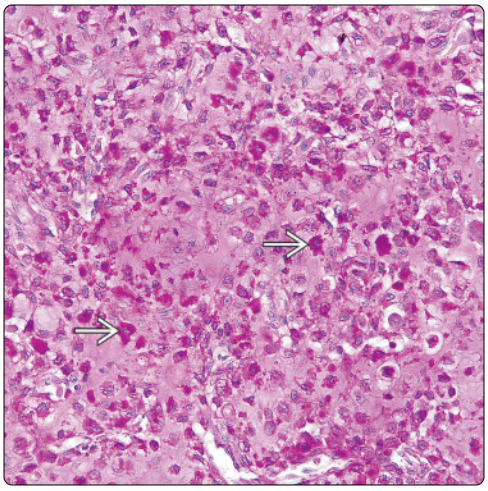


### Cystic Area

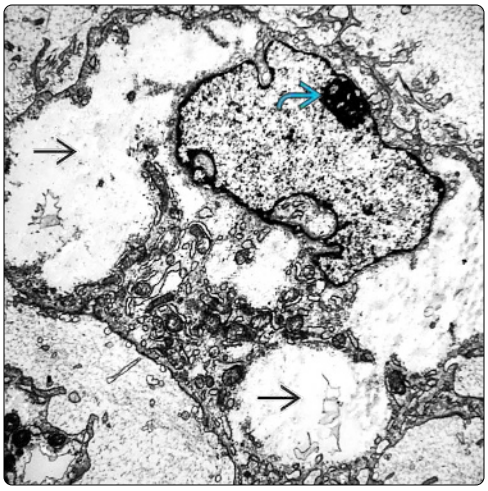


**(Left)** *Sheets of large cells with abundant clear cytoplasm surround a trabeculum of metaplastic woven bone. The woven bone is focally covered by nonneoplastic osteoblasts.* **(Right)** *Cystic component of CC-CSA can mimic an aneurysmal bone cyst. The cyst space is partially filled with blood, and the cyst wall contains linear reactive woven bone.*

### Clear Cells: PAS Positive



### Abundant Glycogen



**(Left)** *CC-CSA is stained with PAS. The neoplastic cells contain abundant PAS-positive glycogen, which fills their cytoplasms and results in a clear appearance on H&E-stained slides.* **(Right)** *Electron micrograph of neoplastic cell of CC-CSA shows abundant ground-glass, membrane free clear zones of intracytoplasmic glycogen. The nucleus is slightly irregular and contains an eccentric nucleolus.*



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# Mesenchymal Chondrosarcoma

KEY FACTS

## TERMINOLOGY

- Rare variant of chondrosarcoma arising in bone and, less commonly, soft tissue

## CLINICAL ISSUES

- Typically affects adolescents and young adults
- Detected as enlarging, sometimes painful mass
- Radical surgery in conjunction with adjuvant radiation and systemic therapy
- 5- and 10-year survival: ~ 55% and 26%, respectively

## IMAGING

- Destructive lytic lesion with scattered speckled calcifications
- Poorly defined margins
- Erodes cortex and extends into soft tissues
- Dark on T1- and bright on T2-weighted images

## MACROSCOPIC

- Solid, gray-tan fleshy with scattered white calcifications
- Destructive and extends into soft tissue

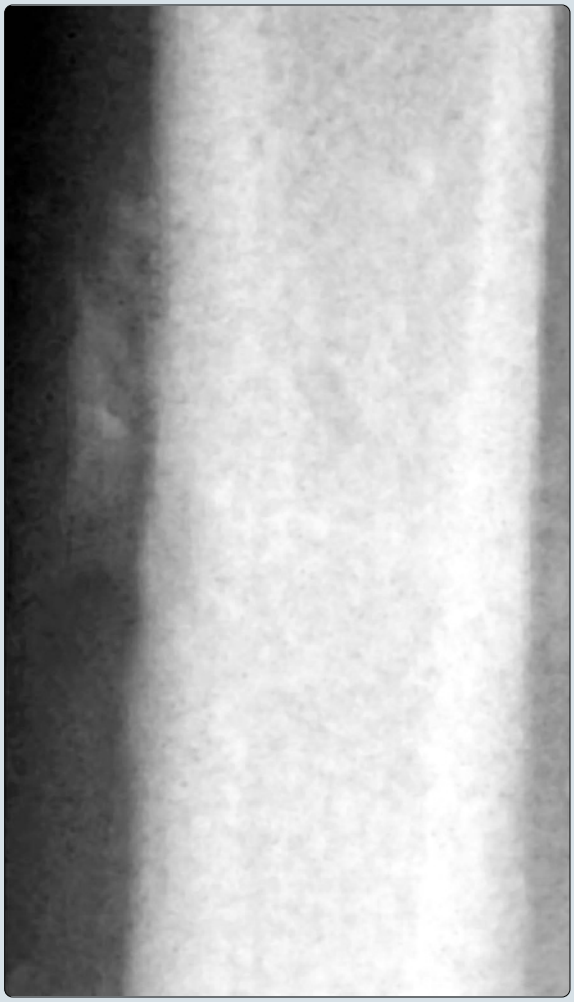
## MICROSCOPIC

- Composed of sheets of small, round, ovoid, or spindle-shaped cells
- Nodules of mildly to moderately cellular hyaline cartilage scattered throughout tumor
  - Cartilage may be sharply demarcated or merge with round cell component
- Hemangiopericytoma-like supportive vascular tree

## ANCILLARY TESTS

- Stains for vimentin, S100 protein, CD99, and SOX9
- Recurrent *HEY1-NCOA2* fusion present

**Parosteal Mesenchymal Chondrosarcoma**



*AP radiograph of the lower leg shows a slightly irregular contour to the periosteal surface of the proximal tibia with reactive bone formation extending into the adjacent soft tissues.*

**Fleshy and Mineralized Mass**



*Resected mesenchymal chondrosarcoma is shown arising on the surface of the tibia. The tumor consists of nodules of focally mineralized gray-tan tissue that is focally fish flesh-like in appearance.*



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## TERMINOLOGY

### Abbreviations

- Mesenchymal chondrosarcoma (MCSA)

### Definitions

- Uncommon subtype of high-grade chondrosarcoma arising in bone and, less commonly, soft tissue

## ETIOLOGY/PATHOGENESIS

### Neoplasm

- Recurrent *HEY1-NCOA2* fusion has been identified in MCSA

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Accounts for ~ 2% of skeletal chondrosarcoma
- Age
  - Typically occurs during 2nd or 3rd decade of life
    - Broad age range of 2-74 years
    - 80% arise in patients between 10-40 years
- Sex
  - No predilection
    - Some series report slight female predominance

### Site

- Most commonly arise in bones of craniofacial skeleton, especially jaw
- Vertebrae, ribs, pelvis, and long bones frequently involved
  - Femur, humerus, tibia most common long bones
    - In long bone, tumor arises in diaphysis

### Presentation

- Symptoms vary according to anatomic site of origin
  - Tumors of spine or cranium may cause neurologic symptoms
- Tumors usually present as enlarging mass that may be painful
- Symptoms may be present for years prior to diagnosis

### Treatment

- En bloc excision with negative margins
- Adjuvant radiation for incompletely excised tumor
- Use of chemotherapy is debatable but often utilized
  - Improved survival related to systemic therapy not proven

### Prognosis

- 5- and 10-year survival: ~ 55% and 26%, respectively
- Prognosis associated with tumors arising in jaw bones is better than other sites
  - 5- and 10-year survival rates: ~ 82% and 56%, respectively
- Lung is most common site of metastasis
  - Metastasis may develop years after initial diagnosis
- Clinical course may be prolonged

## IMAGING

### Radiographic Findings

- Destructive lytic tumor with stippled calcifications
- Poorly defined margins
- Periosteal reaction limited
- Cortical destruction with extension into soft tissue
- Expansion of bone and cortical thickening sometimes noted

### MR Findings

- Heterogeneous with low attenuation on T1-weighted images
- High signal intensity on T2-weighted images

### CT Findings

- Destructive tumor with poorly defined margins and mottled calcifications

### Bone Scan

- Avid uptake with technetium bone scan

## MACROSCOPIC

### General Features

- Solitary, solid, firm, gray-tan, and fleshy
- Scattered areas of gritty, white calcifications
- Usually centered in medullary cavity
  - May arise on surface
    - Destroys cortex and extends into soft tissue

### Size

- Range: 3-22 cm; most > 5 cm

## MICROSCOPIC

### Histologic Features

- Sheets of small, round, ovoid, or spindle cells
  - Contain hyperchromatic nuclei and scant cytoplasm
- Nodules of mildly to moderately cellular hyaline cartilage scattered throughout
- Matrix well demarcated or blends into small cell component
- Cartilage can mineralize or ossify; produces radiodensities on images
- Most cases have extracellular matrix resembling bone
- Vascular tree has hemangiopericytoma-like pattern
- Ultrastructurally round cells are primitive with large nuclei, little cytoplasm, and scattered organelles

## ANCILLARY TESTS

### Immunohistochemistry

- Cartilage cells express vimentin and S100 protein
- Small blue cells stain with vimentin, CD99, LEU-7, neuron-specific enolase, SOX9
  - Staining for desmin and EMA reported
  - SOX9 not expressed in Ewing sarcoma/primitive neuroectodermal tumor and osteosarcoma (except in cartilaginous component in chondroblastic osteosarcoma)
- Chondroid component can stain for ERG, but malignant small round cell component is negative

### Genetic Testing

- Recurrent *HEY1-NCOA2* fusion has been identified in MCSA
- This represents in-frame fusion of *HEY1* to *NCOA2*
  - This is absent in other chondrosarcomas and tumors in differential diagnosis



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- *IDH1* or *IDH2* mutations as seen in conventional cartilaginous tumors is not present in MCSA

## DIFFERENTIAL DIAGNOSIS

### Ewing Sarcoma/Primitive Neuroectodermal Tumor

- Does not contain neoplastic cartilage
- FLI-1 positive
  - Mesenchymal CSA negative
- Contains t(11;22) or variant

### Small Cell Osteosarcoma

- Demonstrates bone formation by tumor cells

### Malignant Lymphoma

- Does not contain chondroid areas
- Shows positive staining for lymphoid markers, which are negative in MCSA

### Rhabdomyosarcoma

- Expresses skeletal muscle markers (MYOD1 and myogenin)

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Arises in unusual locations, e.g., craniofacial bones

### Pathologic Interpretation Pearls

- Malignant round cell tumor with islands of cartilage and hemangiopericytoma-like vascular pattern

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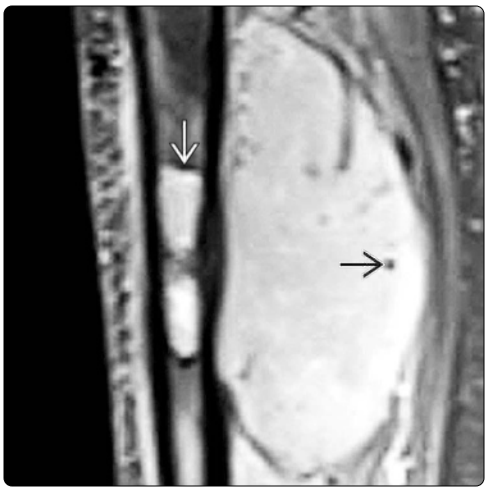



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### Sunburst Periosteal Reaction



### Mesenchymal Chondrosarcoma



**(Left)** *Lateral radiograph of the lower leg shows sclerosis of the proximal tibia with linear and sunburst periosteal reaction posteriorly. There is bone resorption ➔ along the periosteal surface posteroinferiorly and evidence of matrix densities ➔ posteriorly in a large soft tissue mass.* **(Right)** *Sagittal fluid-sensitive T2 sequence MR shows 2 hyperintense signal ➔ areas in the marrow with a large posterior mass. The low signal intensities ⇨ represent matrix calcification.*

### Mineralized Parosteal Tumor



### Large Soft Tissue Mass



**(Left)** *Axial CT scan through the lower leg shows cortical thickening posteriorly along the tibia with destruction along the periosteal surface posteromedially. There is a soft tissue mass posteriorly with matrix radiodensities ➔.* **(Right)** *Axial T1WI MR with fat saturation following intravenous administration of gadolinium shows marrow replacement of the proximal tibia ➔. There is cortical destruction posteriorly with a large, heterogeneously soft tissue mass.*

### Mineralized Mass in Ankle Region



### Tumor in Orbital Region

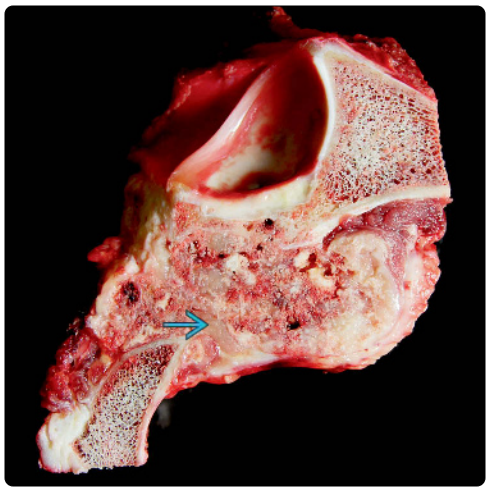


**(Left)** *Mesenchymal chondrosarcoma arising adjacent to or from the surface of the talus ⇨ is shown. The tumor is small, has fluffy mineralizations, and the underlying bone appears to be intact.* **(Right)** *Axial CT scan through the orbital region shows destruction of the frontal bone at the junction of the nasal bone with a small soft tissue component anteriorly ➔. The tumor contains irregular radiodensities, which represent calcification of matrix.*

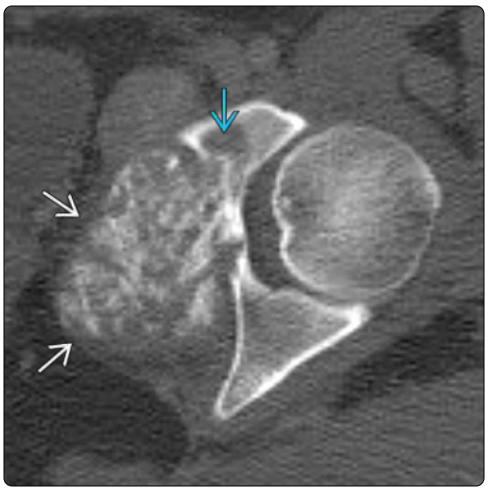


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**Pelvic Mesenchymal Chondrosarcoma**

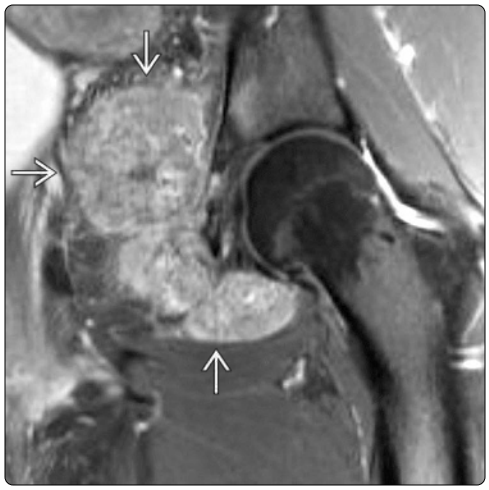


**Mineralized Mass in Pelvis**

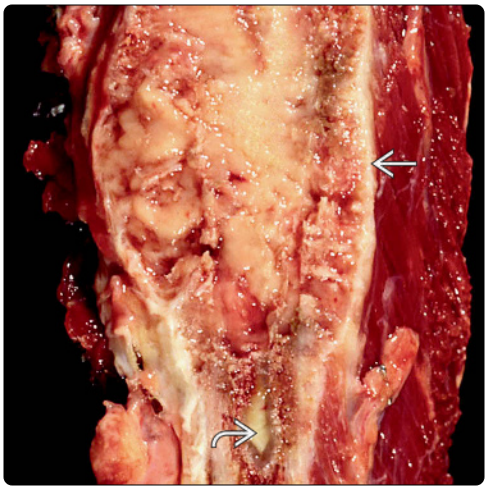


**(Left)** *Large mesenchymal chondrosarcoma arising in the pelvis and extending into soft tissues is shown. The tumor has the typical gross appearance for mesenchymal chondrosarcoma being composed of fleshy tan areas with extensive areas of mineralization.* **(Right)** *Axial CT scan of a mesenchymal chondrosarcoma involving the ilium and adjacent soft tissue is shown. The tumor is large and contains lucent and mineralized areas.*

**Pelvis Mesenchymal Chondrosarcoma**

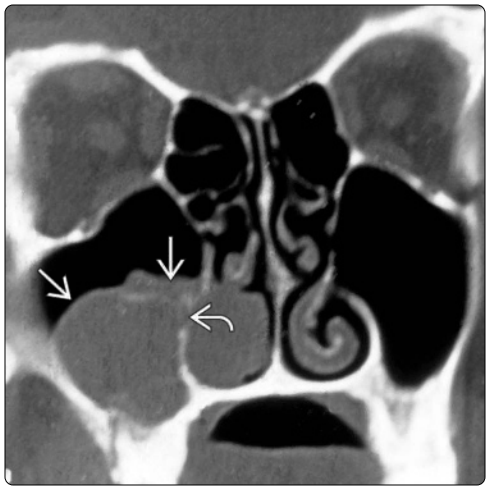


**Fleshy Tumor**

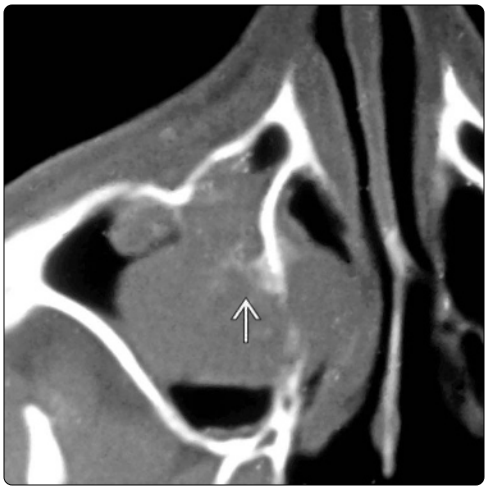


**(Left)** *The corresponding MR scan of the mesenchymal chondrosarcoma involving the pelvic bone and adjacent soft tissue is shown. The tumor is large and has a heterogenous appearance.* **(Right)** *A large mesenchymal chondrosarcoma fills the medullary cavity of the fibula. The pink-tan fleshy tumor destroys the cortex but is confined by the periosteum. The distal portion of the medullary cavity is focally invaded by the growing mass.*

**Tumor Arising in Maxillary Sinus**



**Tumor of Maxilla**

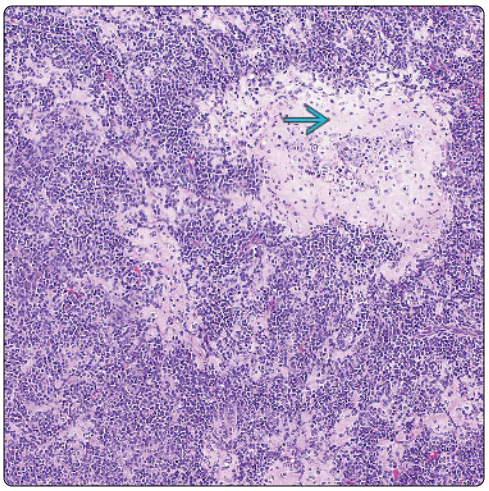


**(Left)** *Coronal CT scan through the face shows a soft tissue mass filling the right maxillary sinus and extending into the nasal cavity. There is destruction of the medial wall of the sinus and erosion of the inferolateral wall.* **(Right)** *Axial CT scan through the maxilla shows a lobulated soft tissue mass with matrix densities extending into the nasal cavity. There is destruction of the medial wall of the sinus with extension to the superior wall of the sinus.*

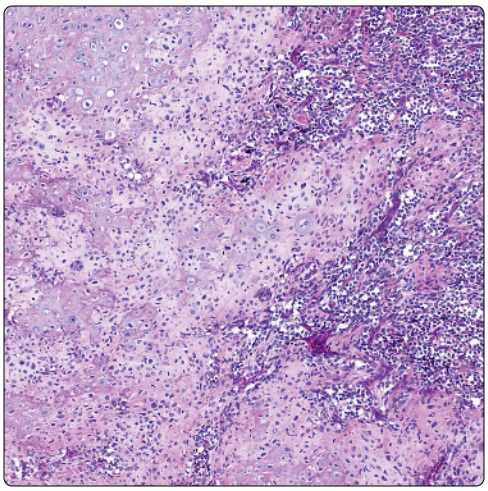


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### Cartilage and Small Round Cells

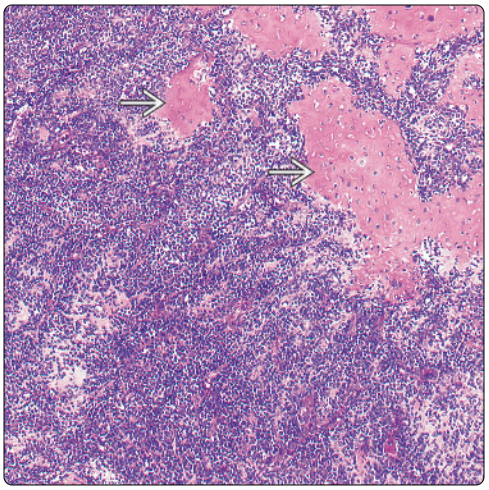


### Prominent Cartilaginous Component

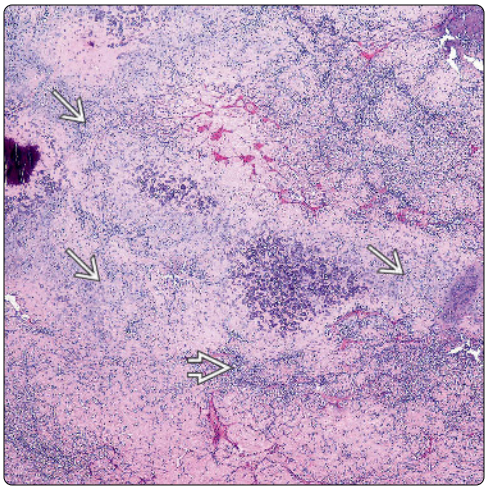


**(Left)** *Typical mesenchymal chondrosarcoma is shown. The tumor is composed of nodules of hyaline-type cartilage that merge imperceptibly with the prominent small round cell component.* **(Right)** *This mesenchymal chondrosarcoma has areas that were composed predominantly of cellular cartilage with only a minor component of the round cell areas.*

### Eosinophilic Cartilage

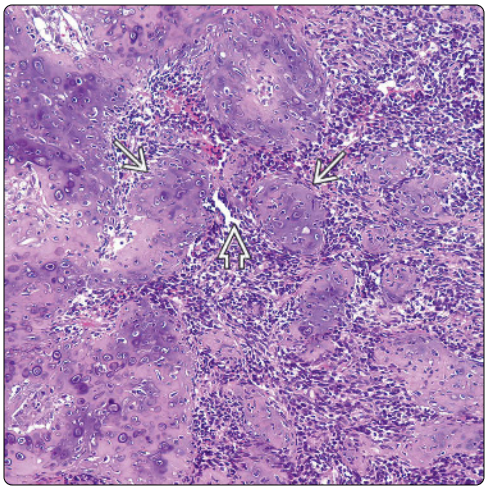


### Abundant Cartilaginous Areas

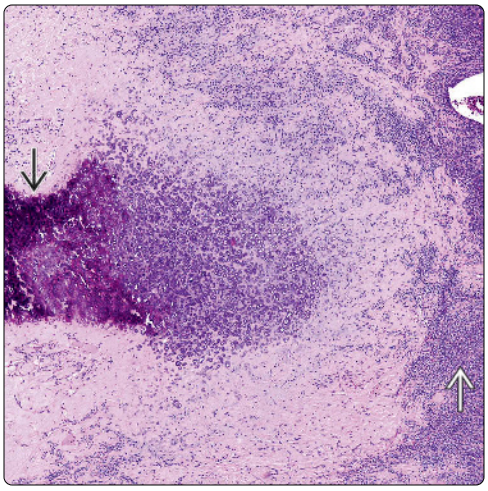


**(Left)** *In this mesenchymal chondrosarcoma, the cartilaginous nodules have a more pink appearance than blue, mimicking bone formation. This should not be confused with osteosarcoma.* **(Right)** *Deposits of cartilage in mesenchymal chondrosarcoma course throughout the tumor. The abundant cartilage obscures the small round cell component and can cause confusion with conventional chondrosarcoma.*

### Nodules of Hyaline-Type Cartilage



### Mineralized Cartilage

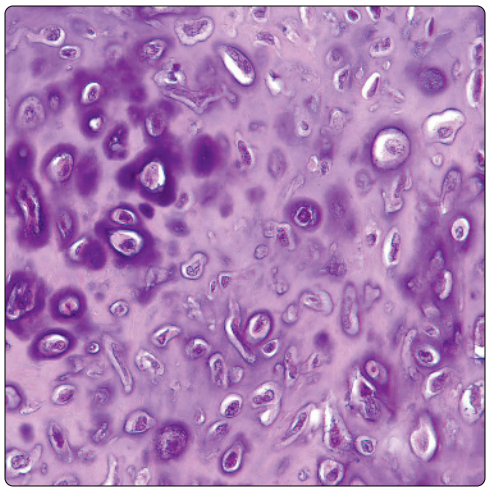


**(Left)** *Mesenchymal chondrosarcoma is seen containing multiple nodules of hyaline cartilage, which focally coalesce to form sheets. The cartilage is surrounded by sheets of small round cells. Scattered branching dilated blood vessels are apparent.* **(Right)** *Large oval nodule of hyaline cartilage in mesenchymal chondrosarcoma is focally mineralized (purple area). The periphery of the nodule is surrounded by a malignant small round cell component.*

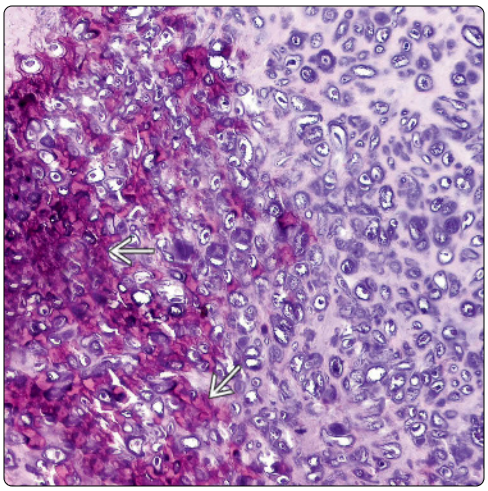


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**Cartilaginous Component**

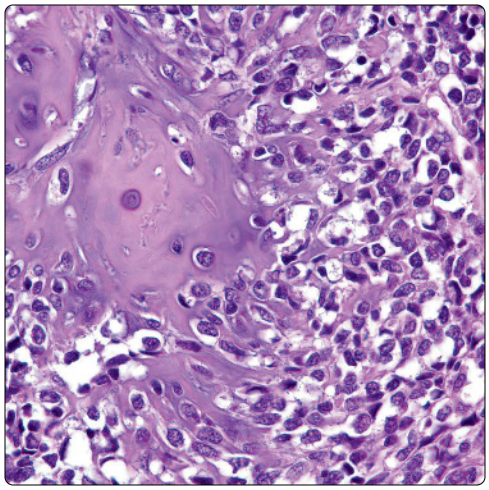


**Cellular Cartilaginous Component**

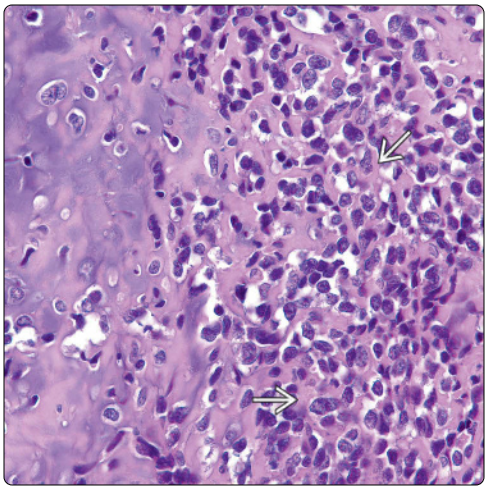


**(Left)** *The islands of cartilage are hyaline in appearance but sometimes may have features reminiscent of fibrocartilage. The cartilage is moderately cellular, and the chondrocytes have enlarged, oval, somewhat vesicular nuclei.* **(Right)** *Neoplastic hyaline cartilage in mesenchymal chondrosarcoma is shown. The cartilage is moderately cellular, and the chondrocytes are relatively small. The matrix is focally calcified, and the calcified regions stain purple and are irregular in configuration ➔.*

**Hyaline Cartilage and Small Round Cells**

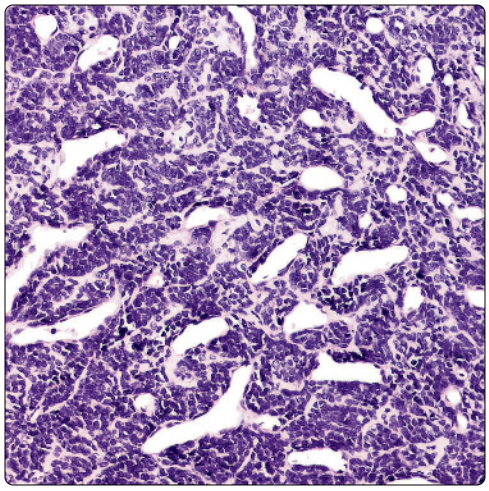


**Osteoid-Like Matrix**

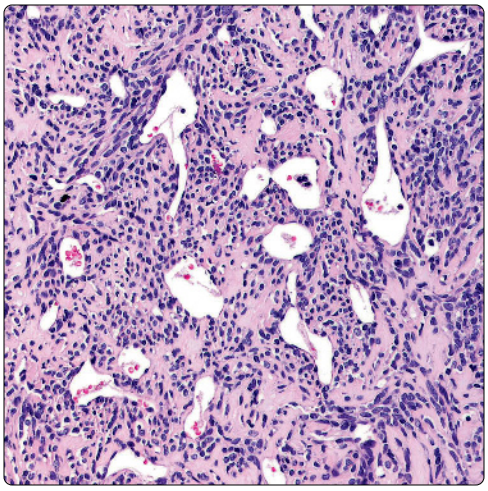


**(Left)** *The hyaline cartilage in mesenchymal chondrosarcoma merges with the small cell component. Peripherally, the matrix diminishes in quantity and surrounds small groups and individual tumor cells. The small cells are round to oval and have fine chromatin and scant contracted pink cytoplasm.* **(Right)** *The purple-blue cartilage matrix in mesenchymal chondrosarcoma becomes eosinophilic and surrounds individual cells ➔. This type of matrix mimics neoplastic bone.*

**Prominent Vasculature**



**Staghorn Pattern**

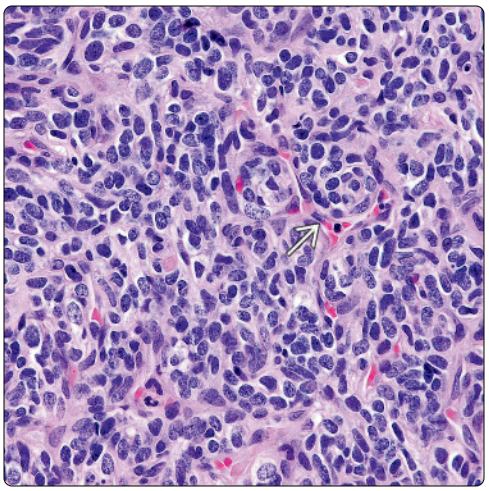


**(Left)** *Mesenchymal chondrosarcoma has a characteristic supportive vascular tree. The vessels are thin walled, mildly dilated, and branch at 45° angles, defining the stag horn or hemangiopericytoma-like pattern. These features are absent in Ewing sarcoma.* **(Right)** *Hemangiopericytoma-like vascular pattern that is typical of mesenchymal chondrosarcoma is shown. The vessels are most prominent in areas populated by the neoplastic small round cells. The round cells are enmeshed in eosinophilic collagen.*

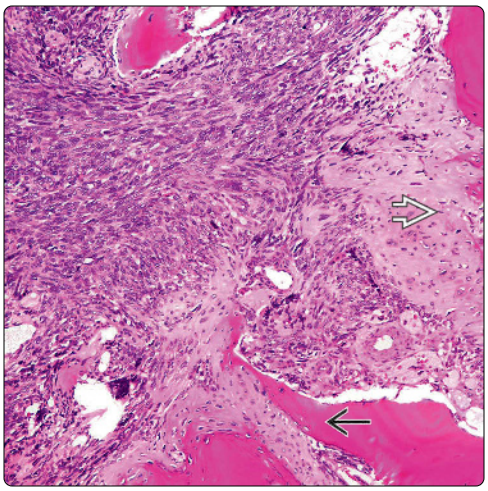


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### Small Round Cell Component

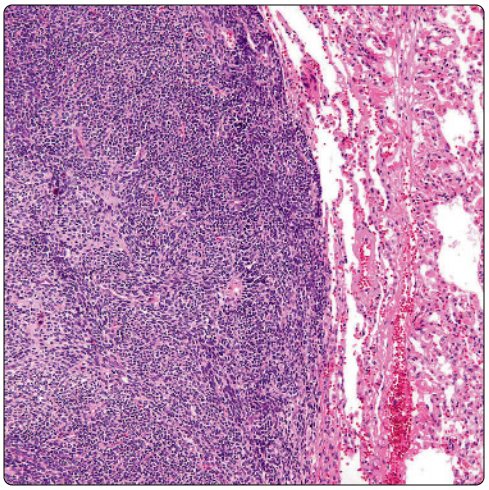


### Infiltrative Growth Pattern

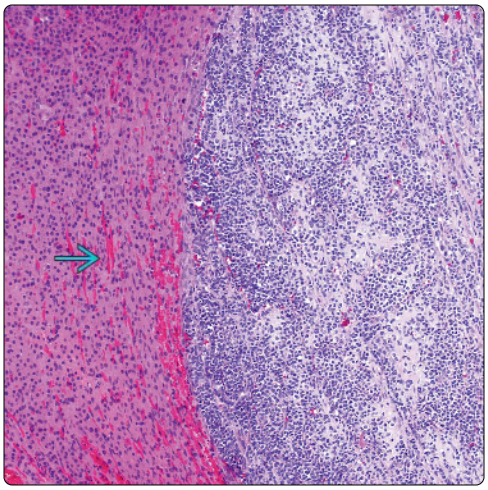


**(Left)** *The vessels in this example are compressed rather than dilated and contain red blood cells. In areas like this, there may be a vague plexiform pattern. The densely packed round cells obscure some of the vascular spaces.* **(Right)** *Mesenchymal chondrosarcoma grows with an infiltrative pattern and invades and envelops preexisting bony trabeculae. The small cells are spindle-shaped and arranged in short fascicles. Some of the neoplastic cartilage is eosinophilic.*

### Metastatic Tumor to Lungs

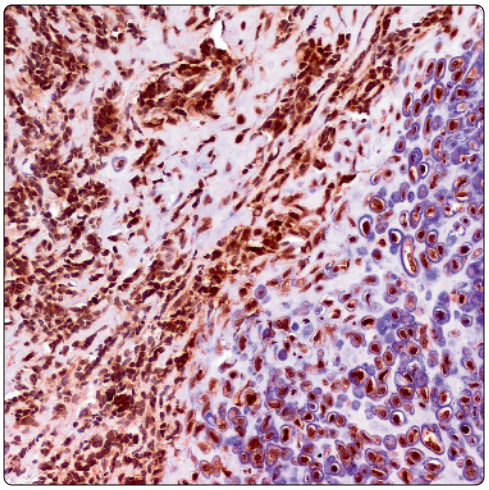


### Metastatic Tumor to Adrenal Gland

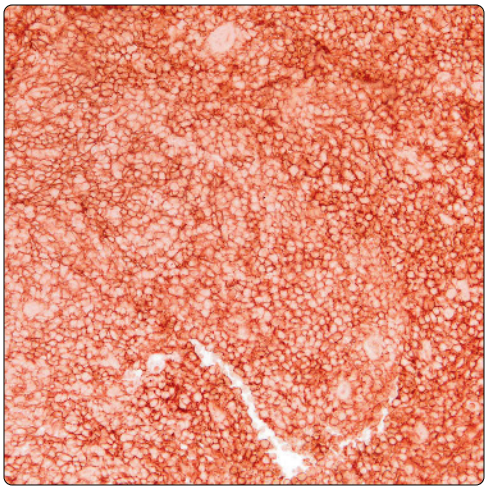


**(Left)** *The lung is a common location for metastases in mesenchymal chondrosarcoma. In this metastasis, the nodule is well demarcated, displaces the parenchyma, and consists solely of the small cell component.* **(Right)** *Mesenchymal chondrosarcoma, unlike many other sarcomas, tends to metastasize to unusual sites. In this example, the tumor has metastasized to the adrenal gland. The patient also had metastatic disease to the pancreas.*

### SOX9 Immunohistochemical Stain



### CD99 Immunohistochemical Stain



**(Left)** *Mesenchymal chondrosarcoma stained with SOX9 nuclear transcription factor is seen associated with cartilage. Both the round cells and chondrocytes show strong nuclear expression. This antibody is helpful in diagnosing cases in which cartilage is not present; however, other tumors, such as Ewing sarcoma (ES), may also stain, so molecular studies, such as FISH, may also be necessary.* **(Right)** *Sheets of round cells in the tumor show strong membranous staining with CD99. Similar staining pattern is also seen in ES.*



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SECTION 5

# Fibrous and Fibrohistiocytic Tumors




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|---|---|
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KEY FACTS

## TERMINOLOGY

- Fibrous cortical defect (FCD): Small lesion limited to cortex
- Nonossifying fibroma (NOF): Mass involves medullary cavity

## CLINICAL ISSUES

- Affects skeletally immature individuals
- Usually asymptomatic and incidental finding
- Often affects metaphysis of distal femur, proximal tibia, and distal tibia
- Observation; curette lesions at risk for fracture

## IMAGING

- Lytic, eccentric, sharp margin with sclerosis, involves cortex and can extend into medullary cavity
- Lobulated contour that may be asymmetric
- Radiographic features characteristic; in most cases biopsy not indicated

## MACROSCOPIC

- Eccentric, red-brown and focally yellow
- Well circumscribed
- Sclerotic borders

## MICROSCOPIC

- Hypercellular with spindle fibroblasts arranged in storiform pattern
- Scattered osteoclast-type giant cells, hemosiderin, and foamy macrophages
- Necrosis and hemorrhage may be present

## DIAGNOSTIC CHECKLIST

- Eccentric metaphyseal lesion in skeletally immature individual: Think NOF
- Hypercellular spindle cell tumor with osteoclast-type giant cells

**Lytic Tumor**



*Oblique radiograph of the distal tibia shows a nonossifying fibroma. The lytic lesion is eccentric and involves the distal diaphysis and metaphysis. The margins are sharp and sclerotic.*

**Solid Red-Brown Mass**



*Nonossifying fibroma fills the medullary cavity of the proximal metaphysis and diaphysis of the fibula. The solid red-brown tumor has resulted in expansion of the bone and thinning of the cortex.*



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## TERMINOLOGY

### Abbreviations

- Fibrous cortical defect (FCD)
- Nonossifying fibroma (NOF)

### Synonyms

- Metaphyseal fibrous defect
- Fibroxanthoma
- Benign fibrous histiocytoma

### Definitions

- Benign fibroblastic proliferation associated with osteoclast-type giant cells
  - FCD: Tumor is limited to cortex
  - NOF: Tumor involves medulla

## ETIOLOGY/PATHOGENESIS

### Developmental Anomaly

- Purportedly nonneoplastic; clonality has not been proven

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Unknown; majority of lesions are asymptomatic
    - ~ 35% of children have ≥ 1 lesions
    - Radiographic studies show 54% of boys and 22% of girls have lesion involving cortex at age 4
- Age
  - Usually diagnosed during 1st-2nd decades of life
    - Peak incidence of FCD: 4-8 years
    - Peak incidence of NOF: 10-15 years
- Sex
  - More common in boys (M:F = 2:1)

### Site

- Arise in metaphysis: 90% in lower extremities
  - Distal femur, proximal tibia, and distal tibia
- Flat or short tubular bones rarely involved
- Majority are solitary; some may be multiple
  - Multiple lesions in neurofibromatosis type 1 and Jaffe-Campanacci syndrome

### Presentation

- Asymptomatic; incidental radiographic finding or pain
- Most common cause of pathologic fracture in children

### Treatment

- Observation or curettage
- Imaging characteristic: Biopsy usually not indicated

### Prognosis

- Excellent; rarely recur

## IMAGING

### Radiographic Findings

- Metaphyseal, eccentric, lytic
- Lobulated asymmetric shape with sharp sclerotic margin; wider and more lytic adjacent to growth plate
- Scalloping of cortex produces trabeculations
- Spontaneous regression: Progressive ossification and incorporation into diaphysis

### MR Findings

- Intermediate to low signal on T1- and T2-weighted images

### CT Findings

- Lucent lesion with sclerotic rim

### Bone Scan

- Mild avidity on technetium scan

## MACROSCOPIC

### General Features

- Eccentric, well circumscribed, oval with sclerotic borders
- Cortex attenuated and may be completely resorbed
- Soft, red brown with areas of yellow discoloration
- Fracture causes extensive hemorrhage and necrosis

### Size

- Usually small; 3-5 cm, may be larger

## MICROSCOPIC

### Histologic Features

- Hypercellular: Plump spindle fibroblasts arranged in storiform pattern
- Mitoses few in number
- Osteoclast-type giant cells scattered throughout
- Hemosiderin and foamy macrophages are common
- Necrosis may be present; especially in setting of fracture

## DIFFERENTIAL DIAGNOSIS

### Giant Cell Tumor of Bone

- Middle-aged adults, epiphyseal-diaphyseal, and large
- Diagnostic mononuclear cells are oval
- Nuclei in giant cells are identical to those of mononuclear stromal cells

### Solid Aneurysmal Bone Cyst

- Solid aneurysmal bone cyst (ABC) and NOF are histologically similar
  - Solid ABC has intratumoral reactive woven bone and less prominent storiform pattern

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Eccentric metaphyseal lesion in skeletally immature individual: Think NOF

### Pathologic Interpretation Pearls

- Bland, spindle-shaped fibroblasts arranged in storiform growth pattern with osteoclast-like giant cells, hemosiderin, and foamy histiocytes

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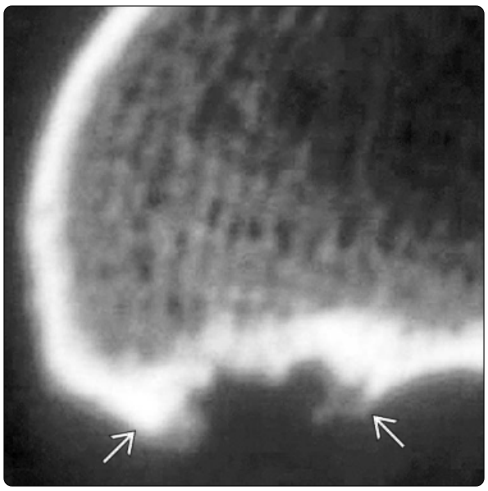



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**Lytic Cortical Lesion**



**Intracortical Lytic**



**(Left)** *A radiograph of the wrist shows a fibrous cortical defect involving the ulnar side of the radius. The tumor is lytic, elongated, has a well-defined, slightly sclerotic margin along the medullary aspect, and is covered by a thin layer of subperiosteal reactive bone.* **(Right)** *Axial CT of a fibrous cortical defect shows the small intracortical soft tissue mass. The tumor is delineated by rebuttressed thickened cortex and does not involve the medullary cavity.*

**Well-Circumscribed Margins**



**Eccentric Lytic**



**(Left)** *AP radiograph of the distal femur shows an oval, lytic lesion with a well-formed sclerotic boundary involving the diametaphyseal region of the distal medial femur. The tumor has a nodular contour and has slightly expanded the bone.* **(Right)** *Lateral radiograph shows a nonossifying fibroma that is eccentrically positioned within the metaphysis of the distal posterior femur. The lytic tumor has minimally expanded the bone and has sclerotic, well-defined margins.*

**Oval Lytic Tumor**



**Sclerotic Margin**



**(Left)** *AP radiograph of the wrist in a child shows a typical nonossifying fibroma of the lateral cortex of the distal radius. Like most lesions of this type, it is eccentric, demarcated by a sclerotic boundary, and results in mild expansion of the diametaphysis.* **(Right)** *Axial CT shows nonossifying fibroma of the radius. The soft tissue density tumor is eccentric, well circumscribed, and has a sclerotic intramedullary margin. The thinned cortex is focally disrupted.*

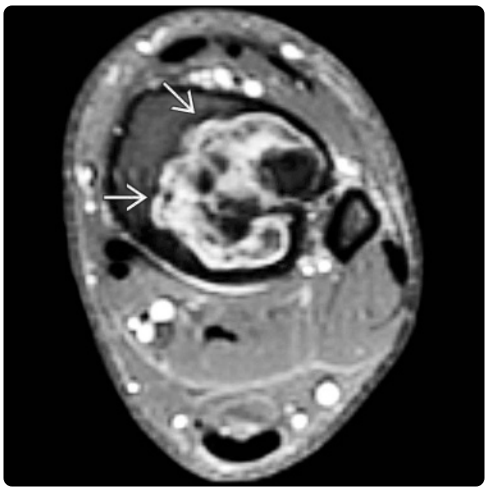


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**Heterogenous Mass**



**Sharply Demarcated Tumor**



**(Left)** *Sagittal T2-weighted MR of a nonossifying fibroma of the distal tibia shows heterogeneous signal intensity. The tumor has a nodular contour, is well delineated, and is surrounded by unremarkable marrow.* **(Right)** *Axial T2-weighted MR shows a nonossifying fibroma that has a heterogeneous signal intensity. The tumor expands the bone and scallops the cortex. The intramedullary margin is delineated by sclerotic bone seen as a dark line ⇨.*

**Large Lytic**



**Multiple Nonossifying Fibromas**



**(Left)** *Oblique radiograph of the distal tibia shows a nonossifying fibroma. The lytic lesion is eccentric and involves the distal diaphysis and metaphysis. The margins are sharp and sclerotic.* **(Right)** *Radiograph shows multiple large nonossifying fibromas ⇨ in a patient with neurofibromatosis. They are lytic, circumscribed, and involve the distal femur and proximal tibia.*

**Sclerotic Margin**



**Edema Around**



**(Left)** *AP radiograph of the lower leg demonstrates the typical features of nonossifying fibroma. The lesion is cortically based (eccentric), elongated in the long axis of the bone, centered in the diametaphysis, and surrounded by a sclerotic wall of reactive bone ⇨. A very small amount of cortical expansion is present.* **(Right)** *T2-weighted MR of a nonossifying fibroma shows edema of the adjacent bone marrow and soft tissues. The prominent edema ⇨ represents a reaction to an occult fracture.*

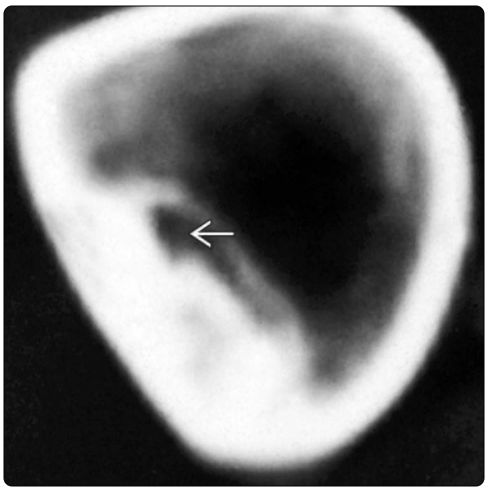


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**Resolving Nonossifying Fibroma**



**Tumor Filling in With Bone**



**(Left)** *Radiograph shows a nonossifying fibroma of the distal femur, which is undergoing resolution. The tumor is being replaced by reactive bone* ➡ *that is being deposited in the receding mass. The ossified portion is well delineated and merges with the overlying cortex.* **(Right)** *Axial CT shows a nonossifying fibroma that is undergoing resolution. The tumor is being replaced by reactive bone, but a small portion of the intramedullary component remains and is lytic* ➡.

**Pathologic Fracture**

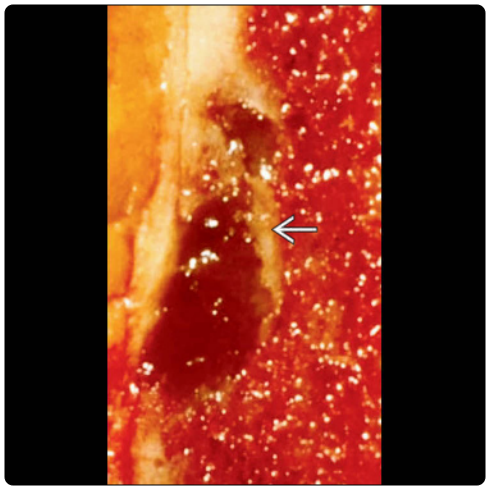


**Fractured Tumor With Hardware**

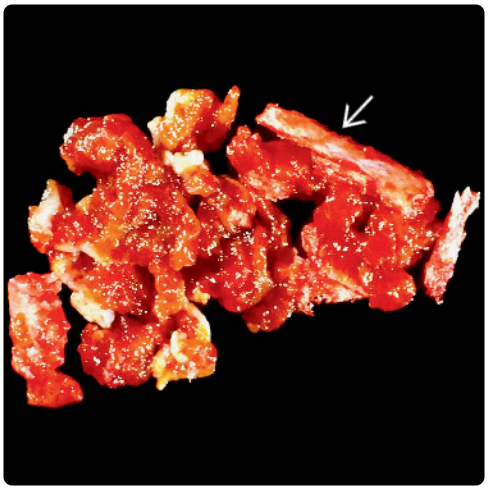


**(Left)** *Radiograph of the distal femur shows a pathological fracture through a nonossifying fibroma. The lesion is somewhat obscured by the fracture, but the proximal end of the sclerotic wall that demarcates the upper end of the lesion* ➡ *can be seen at the distal end of the upper fracture fragment.* **(Right)** *Fluoroscopic image shows nonossifying of the distal femur that had fractured and is repaired with a lateral plate and screws. The large lytic tumor* ➡ *has expanded the femur.*

**Small Nonossifying Fibroma**



**Curettage Specimen**



**(Left)** *A small nonossifying fibroma of the distal femur involves the cortex and medullary cavity. The tumor is solid, red-brown, and sharply marginated by a shell of reactive bone* ➡. **(Right)** *Curettage specimen shows a nonossifying fibroma removed from a long bone. The tan-red-brown fragments of solid tumor are admixed with pieces of bone. The fragment of cortex removed to gain access to the medullary canal is visible* ➡.

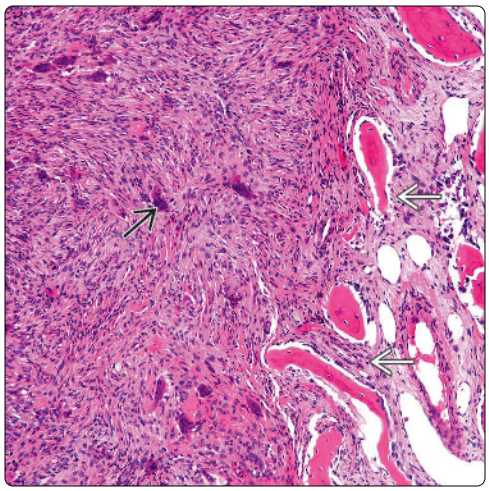


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### Sharp Margin With Cortex

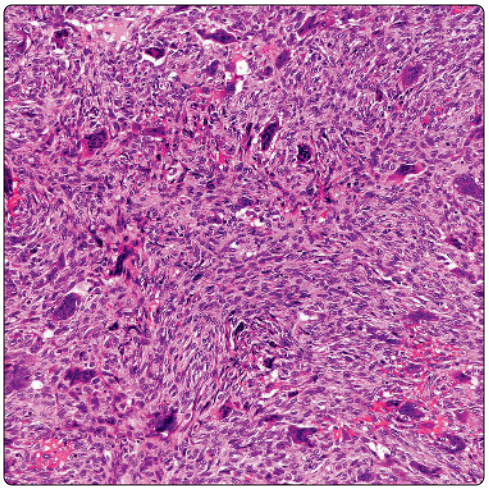


### Adjacent Reactive Woven Bone

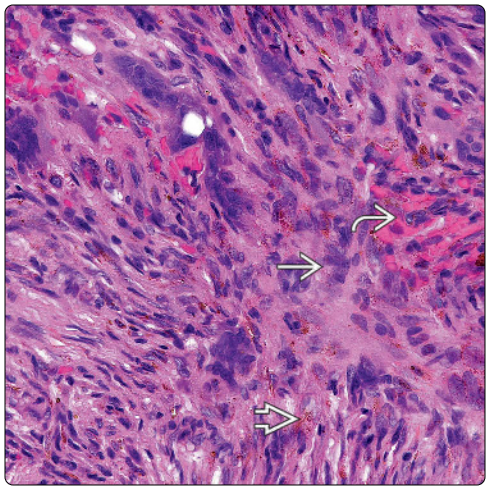


**(Left)** *This fibrous cortical defect involving most of the cortex is covered by thickened periosteum. The tumor has jagged but sharp margins with the surrounding cortex; the medullary cavity is uninvolved.* **(Right)** *This nonossifying fibroma is sharply demarcated from the medullary cavity by a rim of reactive woven bone. The cellular tumor is solid and contains scattered, multinucleated osteoclast-type giant cells.*

### Storiform Pattern

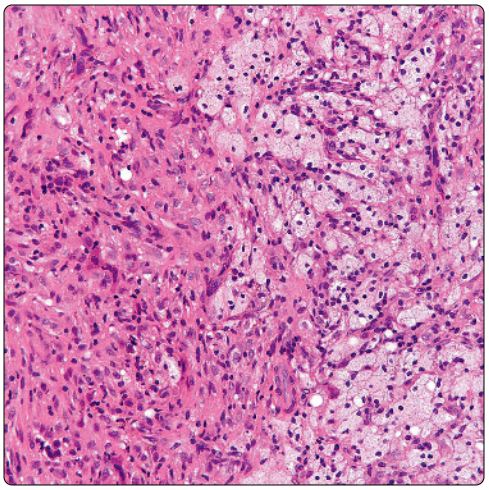


### Spindle Cells With Hemosiderin

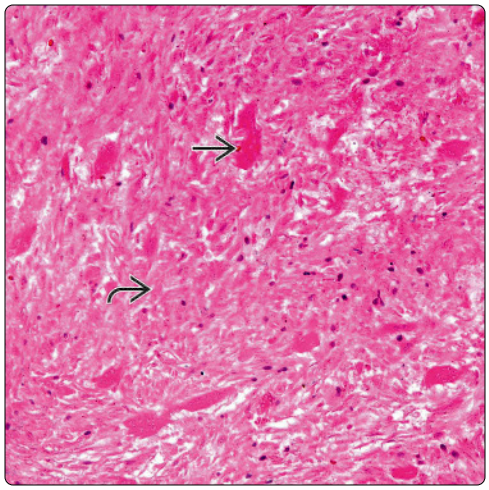


**(Left)** *Typical nonossifying fibroma is shown that is cellular and contains scattered osteoclast-type giant cells. The spindled tumor cells are arranged in intersecting fascicles forming a storiform pattern. Occasional aggregates of extravasated red blood cells are present.* **(Right)** *Nonossifying fibroma is composed of spindle cells oriented in a focal storiform pattern and scattered osteoclast-type giant cells. Often present are golden brown hemosiderin deposits and small foci of hemorrhage.*

### Foamy Macrophages



### Necrotic Nonossifying Fibroma



**(Left)** *Many foamy macrophages are present in this nonossifying fibroma. The clusters of cells are adjacent to proliferating spindle cells of the tumor.* **(Right)** *A nonossifying fibroma has undergone pathologic fracture and secondary necrosis. The visible tumor ghost cells consist of the typical admixture of spindle cells arranged in fascicles and osteoclast-type giant cells.*



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# Desmoplastic Fibroma

KEY FACTS

## TERMINOLOGY

- Locally aggressive tumor believed to be intraosseous counterpart of deep-seated soft tissue fibromatosis

## CLINICAL ISSUES

- Rare: Accounts for 0.1% of primary bone tumors
- Most often develops during 2nd or 3rd decade of life
- Originates in metaphyses of long bones & in mandible
- Slow growing
- Painful
- Complete local excision
- High rate of recurrence following curettage

## IMAGING

- Radiolucent
- Honeycomb or bubbly appearance
- Well-delineated margin

## MACROSCOPIC

- Oblong & well circumscribed
- Solid, rubbery, tan-white

## MICROSCOPIC

- Similar to soft tissue fibromatosis with variable cellularity & regions of abundant collagen deposition
- Neoplastic cells are spindle fibroblasts arranged in broad sweeping fascicles
- Uniform cytologically bland spindle cells

## ANCILLARY TESTS

- No specific immunoprofile
- Unlike soft tissue fibromatosis, desmoplastic fibroma (DF) very rarely shows nuclear staining for β-catenin
  - β-catenin pathway is not as important in pathogenesis of DF
  - No increase in incidence of colon cancer, & patients do not have other stigmata of Gardner syndrome

**Destructive Mass**



*Desmoplastic fibroma presents in the fibula as an elongated, expanded, bubbly, lytic tumor. The proximal and distal margins are well circumscribed, and a periosteal shell of bone is present.*

**Large, Solid, Tan Tumor**



*Desmoplastic fibroma of the fibula is solid, tan-white, and rubbery with well-circumscribed margins. The tumor expands the bone and is delineated by an eggshell-like layer of subperiosteal bone.*



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## TERMINOLOGY

### Abbreviations

- Desmoplastic fibroma (DF)

### Synonyms

- Intraosseous fibromatosis; intraosseous desmoid tumor

### Definitions

- Locally aggressive, nonmetastasizing fibroblastic neoplasm analogous to soft tissue deep-seated fibromatosis

## ETIOLOGY/PATHOGENESIS

### Neoplasm

- Mutation in mesenchymal stem cells

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - One of rarest primary bone tumors; accounts for < 0.1% of primary bone tumors
- Age
  - Wide age range from young children to elderly
  - Peak incidence in 2nd or 3rd decade of life; 75% of patients < 30 years
- Sex
  - Equal gender distribution

### Site

- Most frequently develops in metaphyses of long bones, mandible, & pelvis; rarely juxtacortical or spinal involvement

### Presentation

- Pain & swelling; progressive expansion of involved bone
- Headache, recurrent otitis, & hearing loss with tumors in craniofacial skeleton; rarely presents as pathologic fracture

### Treatment

- Complete local excision is treatment of choice; en bloc excision or aggressive curettage

### Prognosis

- Significant rate of recurrence following curettage; much lower after complete excision

## IMAGING

### Radiographic Findings

- Radiolucent; expansile with well-defined borders
- Often characteristic honeycomb, trabeculated, or bubbly appearance
  - Caused by endosteal ridges of thickened cortex between lobules of tumor
- Erosion of cortex with extension into soft tissue; limited or no periosteal reaction

### MR Findings

- Intermediate signal on T1-weighted images; isointense or hypointense to skeletal muscle; heterogeneous on T2-weighted images

### CT Findings

- Radiolucent, well defined; helps to identify extent of tumor

### Bone Scan

- Increased avidity on technetium scan

## MACROSCOPIC

### General Features

- Oblong & well circumscribed, tan-white
- Leathery or rubbery; similar in consistency to soft tissue fibromatosis; can erode cortex & extend into soft tissue

### Size

- Usually 5-10 cm in greatest dimension

## MICROSCOPIC

### Histologic Features

- Similar to soft tissue fibromatosis with variable cellularity & regions of abundant collagen; stroma can be loose & myxoid
- Neoplastic cells are uniform, bland spindle fibroblasts/myofibroblasts arranged in broad fascicles; stellate cells populate myxoid regions
- Stroma may contain small-caliber blood vessels & foci of extravasated red blood cells; mitoses few in number & of normal configuration
- Focal infiltration can be seen at periphery; extensive infiltration should raise concern for fibrosarcoma or low-grade fibroblastic osteosarcoma

## ANCILLARY TESTS

### Immunohistochemistry

- No specific immunohistochemical profile
- Unlike soft tissue fibromatosis, DF very rarely shows nuclear staining for β-catenin

## DIFFERENTIAL DIAGNOSIS

### Well-Differentiated Osteosarcoma

- Each composed of bland spindle cells arranged in fascicles; osteosarcoma contains neoplastic bone; infiltrates preexisting cancellous bone
- MDM2 & CDK4 stain well-differentiated osteosarcoma but not DF

### Well-Differentiated Intramedullary Fibrosarcoma

- Grows with permeative pattern & is more cellular; often arranged in herringbone pattern & demonstrates greater degree of nuclear atypia with more frequent mitoses

### Fibrous Dysplasia

- Cells arranged in storiform pattern & not broad fascicles; contains curvilinear trabeculae of woven bone, which is not feature in DF

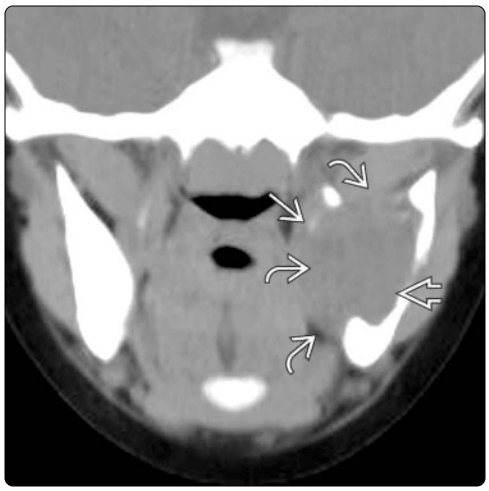
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### Desmoplastic Fibroma of Mandible



### Cortical Destruction



**(Left)** *Coronal CT of a desmoplastic fibroma shows a soft tissue mass that expands and destroys the left mandibular ramus. The tumor is similar in density to skeletal muscle and has a sharp margin with the residual bone. A small focus of peripheral reactive bone is present.* **(Right)** *Axial CT shows a desmoplastic fibroma of the mandibular condyle. The tumor destroys the cortex medially and bulges into the soft tissues. The interface with bone is sharp.*

### Lobulated and Lytic

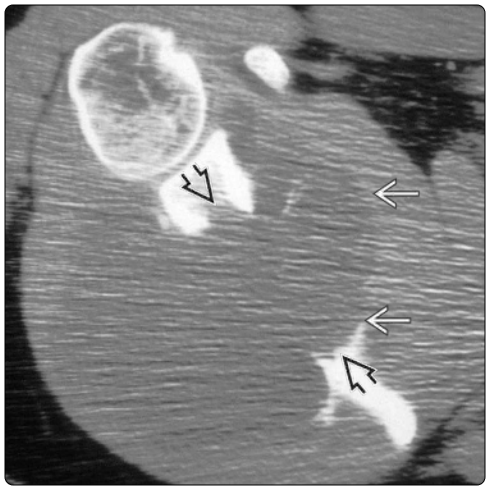


### Bubbly Appearance

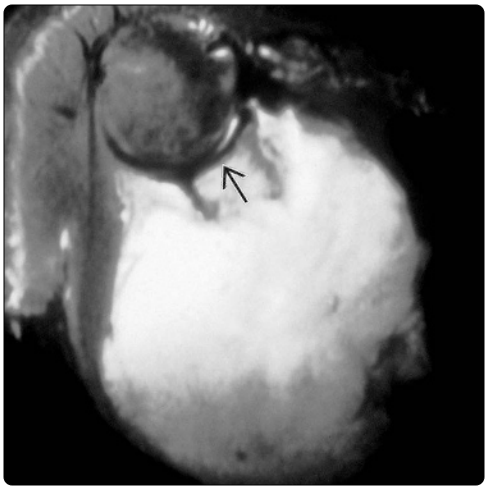


**(Left)** *A desmoplastic fibroma presents as a loculated, lytic lesion in the distal radius. The margins are sharp and sclerotic and the pressure effect on the adjacent ulna is from an associated soft tissue mass.* **(Right)** *A desmoplastic fibroma that produces a bubbly, lytic mass with well-defined margins extends to the base of the articular surface. The cortex is thinned and expanded. The endosteal ridges caused by the tumor manifest as lines that course through the tumor.*

### Low-Density Mass of Scapula



### Hyperintense on T2-Weighted MR

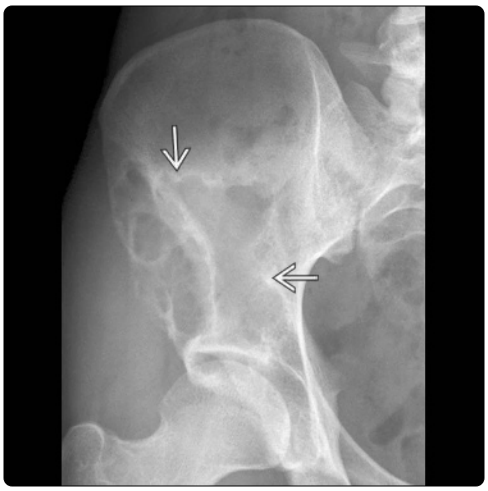


**(Left)** *Axial CT scan of a desmoplastic fibroma shows a low-density mass that has destroyed the scapula body with expansion of the bone. Periosteal new bone is seen at the margins. The intraosseous margins are well demarcated.* **(Right)** *T2-weighted axial MR with fat saturation shows a hyperintense desmoplastic fibroma within the scapula. The tumor expands into the anterior and posterior soft tissues. The marrow replacement suggests extension to the articular margin.*



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### Lobulated and Expanded Lesion of Ilium



### MR of Desmoplastic Fibroma



**(Left)** *Desmoplastic fibroma of the ilium presents as a lobulated, expanded lesion in the supraacetabular region. The tumor is lytic, trabeculated, and has well-circumscribed sclerotic margins.* **(Right)** *T1-weighted coronal MR of a desmoplastic fibroma shows marrow replacement of the right ilium by a lesion that has expanded the lateral acetabular wall. The margins are well defined and no reactive changes are visible in the adjacent normal fatty marrow.*

### Lucent and Lobulated Lesion

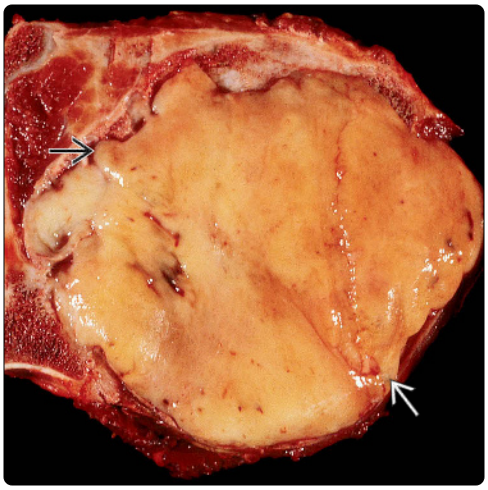


### Acetabular Desmoplastic Fibroma

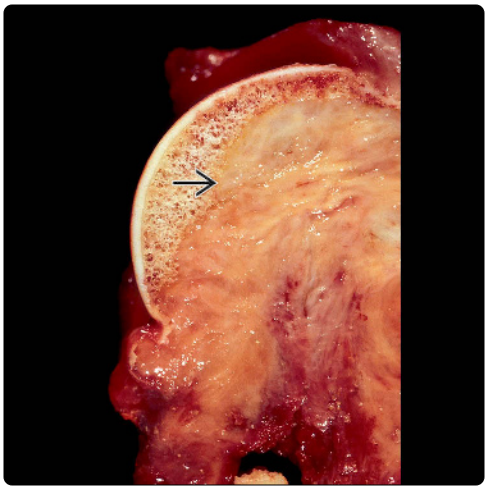


**(Left)** *A desmoplastic fibroma presents as a vague, lucent, lobulated lesion in the right medial acetabulum with thick, reactive sclerosis along the supraacetabular ilium. There is no cortical destruction. The inferior margin is not well defined.* **(Right)** *CT shows a desmoplastic fibroma in the right medial acetabulum that has the density of soft tissue and is surrounded by a thick, sclerotic margin. The tumor extends superiorly with irregular, tentacle-like extension.*

### Solid, Rubbery, Tan Tumor



### Well-Demarcated, Tan, Solid Mass

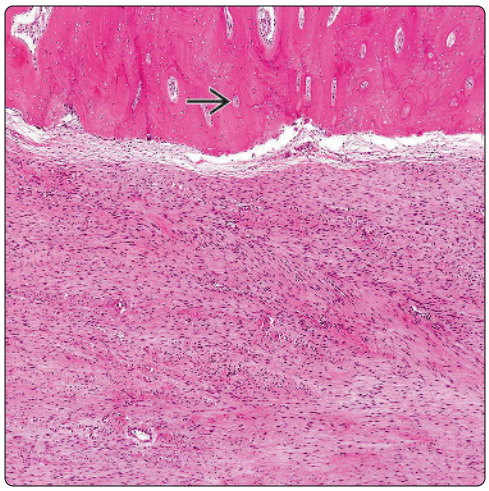


**(Left)** *Desmoplastic fibroma is predominately solid, rubbery, and tan; it has a well-circumscribed sclerotic margin, and there is a shell of subperiosteal new bone. The tumor results in the resorption of the underlying preexisting bone.* **(Right)** *Desmoplastic fibroma of the proximal humerus appears as a focally hemorrhagic, solid, tan-white striated mass. The tumor has a well-demarcated margin and has resulted in cortical destruction and extension into the adjacent soft tissues.*

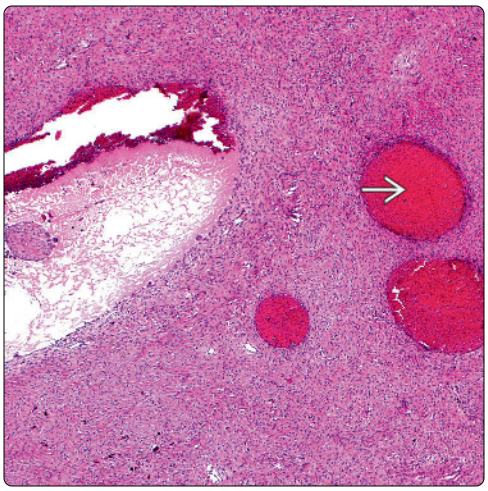


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### Periphery of Desmoplastic Fibroma

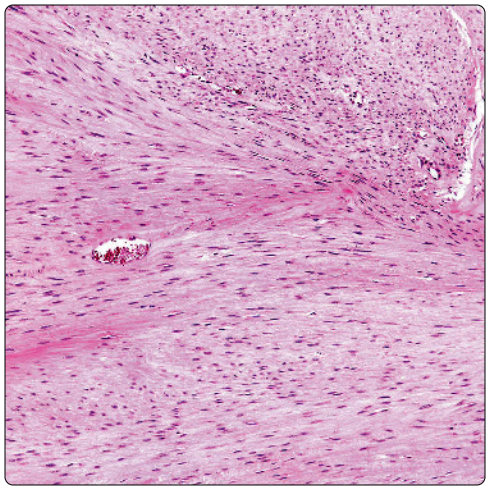


### Cystic Changes

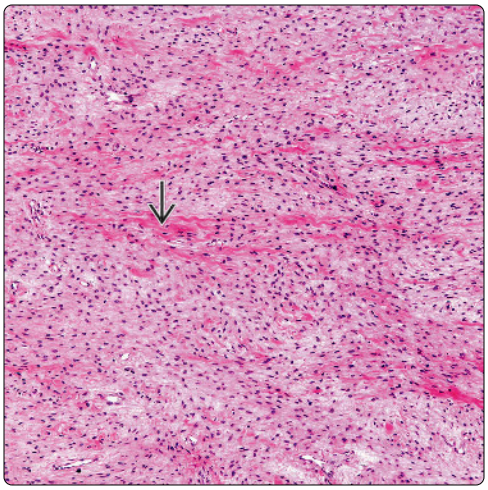


**(Left)** *The peripheral aspect of a desmoplastic fibroma shows its sharp interface with the adjacent sclerotic reactive woven bone ⇨. This relationship is the histologic counterpart to the sclerotic well-defined margin seen on radiographs. The tumor is uniform and relatively hypocellular.* **(Right)** *This desmoplastic fibroma is moderately cellular and in this example has some scattered, small, blood-filled cystic spaces ➡. The tumor is otherwise homogeneous and uniformly cellular.*

### Fascicles of Spindle Cells

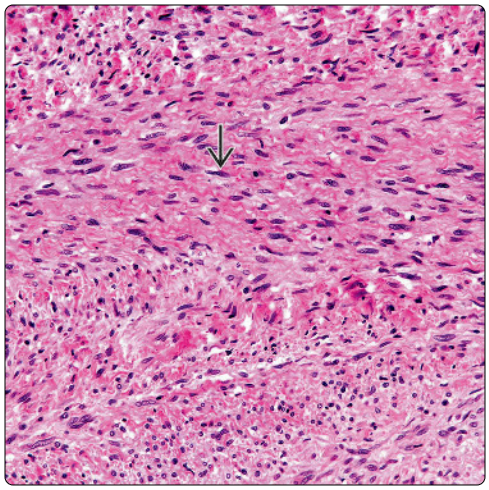


### Spindle and Stellate Tumor Cells

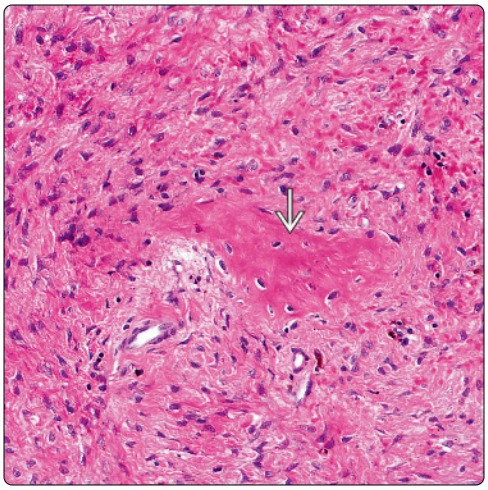


**(Left)** *A desmoplastic fibroma is composed of fascicles of uniform, spindle-shaped cells associated with pink extracellular collagen fibers. The fascicles are broad and sweeping, and the cellularity is moderately dense.* **(Right)** *Desmoplastic fibroma is composed of spindle and stellate-shaped fibroblasts that are surrounded by variable amounts of collagen. The neoplastic cells are cytologically banal, and the collagen fibers range from fine-appearing fibrils to thick, ropey undulating bundles ⇨.*

### Bland-Appearing Spindle Cells



### Reactive Bone Formation

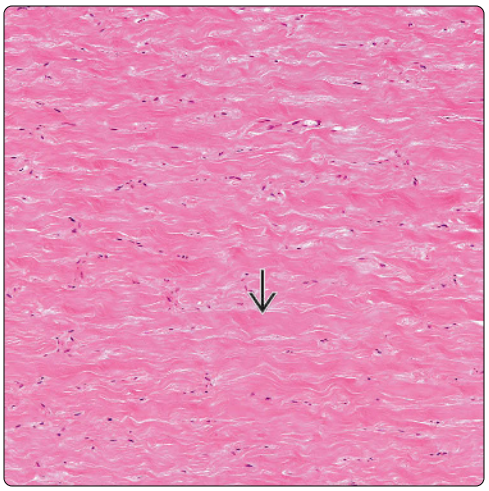


**(Left)** *Desmoplastic fibroma is generally moderate to hypocellular and is composed of spindle and stellate-shaped tumor cells ⇨. The spindle cells may be arranged in intersecting fascicles and are associated with adjacent collagen fibers. Necrosis is usually absent or minimal.* **(Right)** *Recurrent desmoplastic fibroma contains reactive woven bone ➡. The presence of the bone raises the differential diagnosis of fibrous dysplasia, which, out of context, can cause diagnostic challenges.*

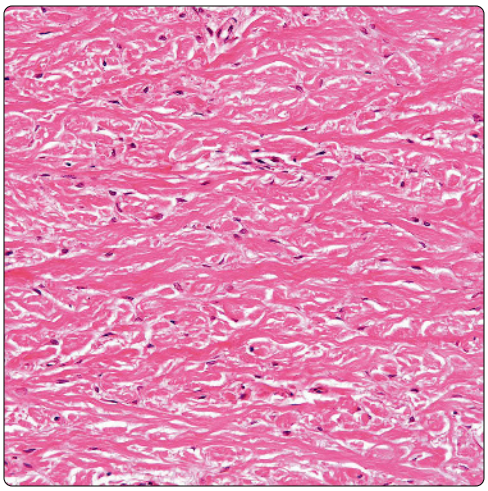


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### Collagenous Stroma

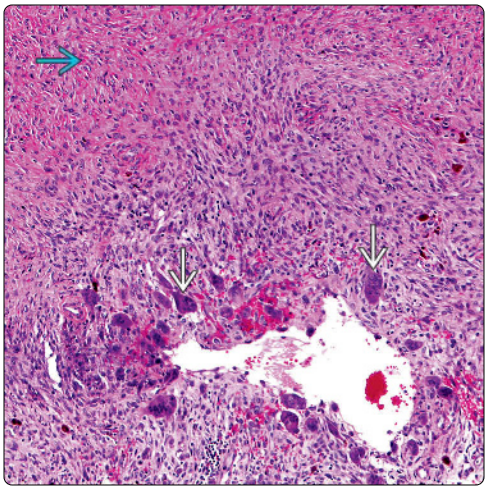


### Collagenous Stroma With Ropey Fibers

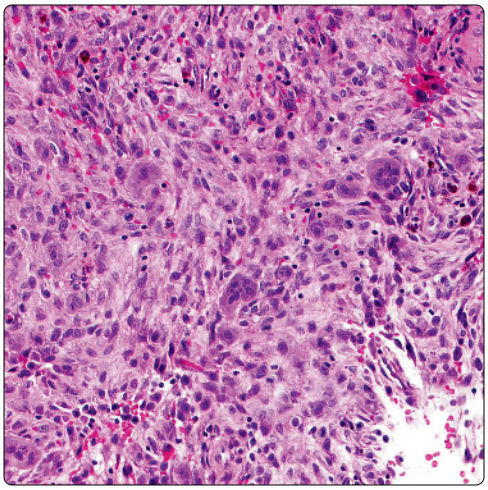


**(Left)** *Desmoplastic fibroma, as the name implies, may contain abundant collagen. In this case, the collagen fibers are large, somewhat keloidal-like in appearance, and are deposited in a parallel fashion ⇨. The neoplastic cells are bland and inconspicuous.* **(Right)** *In this example of a desmoplastic fibroma, the collagen fibers are deposited in a weave-like pattern. They obscure the small and cytologically bland tumor cells. The spaces in between the collagen fibers are artifactual.*

### Cystic Changes With Giant Cells

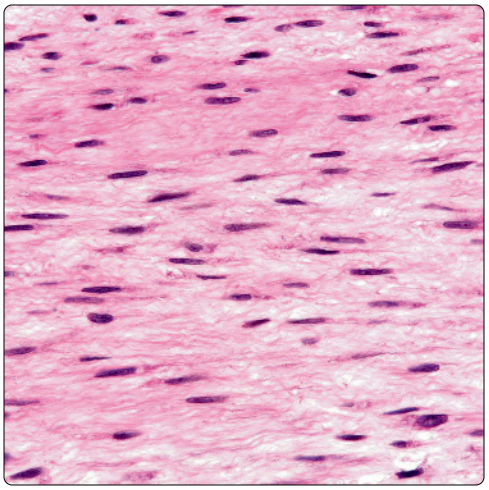


### Cyst Wall With Blood and Giant Cells

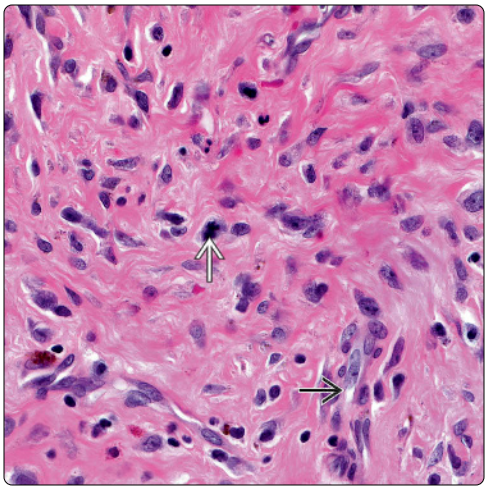


**(Left)** *This desmoplastic fibroma has a focus of increased cellularity that is associated with a small aneurysmal bone cyst-like focus with hemorrhage. The blood induces the influx of osteoclast-type giant cells ➡. Adjacent to this area, the tumor has the features characteristic of desmoplastic fibroma ⇨.* **(Right)** *This is a cellular focus within an otherwise characteristic desmoplastic fibroma. The increased cellularity is from hemorrhage, giant cells, scattered lymphocytes, and reactive fibroblasts.*

### Uniform Cytology



### Mitotic Figure



**(Left)** *The neoplastic cells in desmoplastic fibromas are arranged in fascicles and associated with undulating collagen fibers. The tumor cells are uniform and spindle-shaped and have elongated nuclei with rounded or pointed ends. The cytoplasm is indistinct and eosinophilic.* **(Right)** *In this desmoplastic fibroma, there is a whorling growth pattern and scattered blood vessels ⇨. A mitotic figure ➡ is present, which is usually not numerous in desmoplastic fibroma.*



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KEY FACTS

## TERMINOLOGY

- Uncommon myofibroblastic tumor

## CLINICAL ISSUES

- Usually presents at birth, during infancy, or in early childhood
- Males affected more frequently than females
- Solitary tumors more frequent than multiple lesions
- Frequently involves skull, jaw, ribs, and pelvis
- Asymptomatic or may cause pathologic fracture
- Prognosis excellent for patients without visceral involvement
- Simple excision usually curative
- Patients with multiple visceral lesions, especially those with involvement of gastrointestinal tract, may have fatal outcome from severe hemorrhage

## IMAGING

- Benign appearance
- Oval or elongated
- Well-circumscribed sclerotic margins

## MACROSCOPIC

- Firm
- Well delineated
- Tan-white

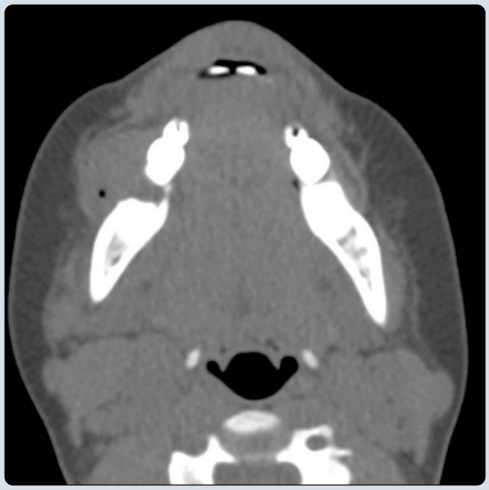
## MICROSCOPIC

- Whorling or nodular growth pattern
- Central zone of primitive-appearing, round to short spindled cells with hemangiopericytomatous vasculature
- In peripheral zone, neoplastic cells are myoid appearing

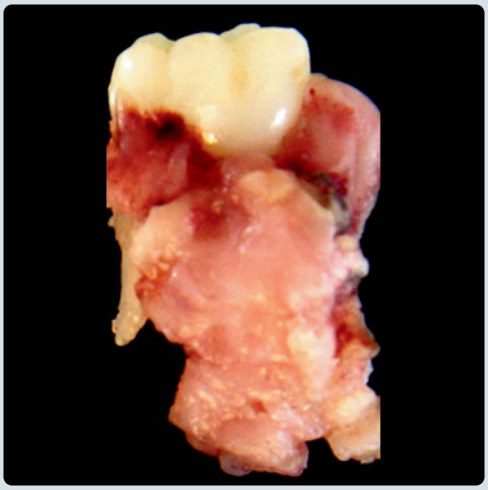
## DIAGNOSTIC CHECKLIST

- Think myofibroma for benign spindle cell tumor in young child

**Myofibroma of Mandible**



**Pink-Tan Tumor Adjacent to Tooth**

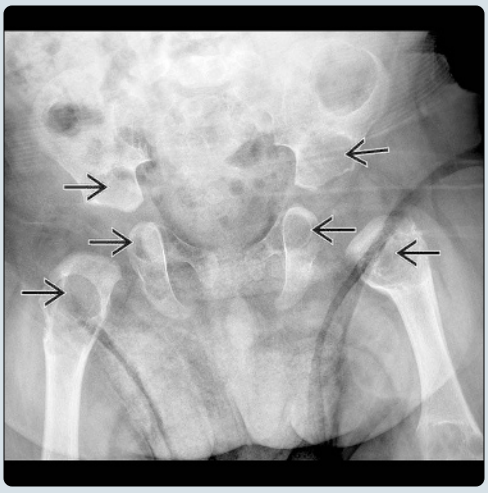


**(Left)** *Axial CT scan of an intraosseous myofibroma shows a lytic lesion involving the right mandible. The lesion has well-defined margins with the bone and extends into soft tissue. No mineralization is present.* **(Right)** *Intraosseous myofibroma arises in the mandible adjacent to the teeth and has a homogeneous, tan-pink cut surface. The teeth adjacent to the tumor are unremarkable.*

**Multiple Myofibromas**



**Myofibromatosis of Skeleton**



**(Left)** *In this radiograph, multiple myofibromas are present in the humerus and proximal ulna. The tumors are lytic and well circumscribed, and some have sclerotic margins.* **(Right)** *Radiograph of the pelvis in this infant shows myofibromatosis. The oval lytic tumors are present in the femurs, ischia, and ilia.*



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## TERMINOLOGY

### Synonyms

- Infantile myofibromatosis
- Congenital generalized fibromatosis

### Definitions

- Uncommon benign neoplasm composed of bland, spindle-shaped cells showing myofibroblastic differentiation
- Lesions can be single (myofibroma) or multiple (myofibromatosis)

## ETIOLOGY/PATHOGENESIS

### Neoplastic

- Etiology is unknown

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Rare
- Age
  - Usually presents at birth, during infancy, or early childhood
  - Rare cases have been reported in adults
- Sex
  - Males affected more frequently than females

### Site

- Manifests as single or multiple lesions
  - Solitary tumors more frequent and may involve bone, soft tissue, or skin
  - When multiple, can involve skeletal and extraskeletal sites, including skin, soft tissues, and viscera
- Frequently involves skull, jaw, ribs, and pelvis
- In long bones, often centered in metaphysis

### Presentation

- May be asymptomatic or painful
- Palpable mass
- May cause pathologic fracture

### Treatment

- Simple excision usually curative

### Prognosis

- Excellent for patients without visceral involvement
- Patients with multiple visceral lesions involving gastrointestinal tract or lungs may have fatal hemorrhage

## IMAGING

### Radiographic Findings

- Oval or elongate
- Lucent and eccentric
- Well-circumscribed sclerotic margins
- May erode or expand bone

### MR Findings

- Low signal on T1WI and heterogeneous on T2WI
- Enhances peripherally with gadolinium

### CT Findings

- Lytic, well circumscribed
- Hypo- to isointense to skeletal muscle with peripheral enhancement with contrast

## MACROSCOPIC

### General Features

- Firm, tan-white, well delineated

## MICROSCOPIC

### Histologic Features

- Central regions often hypercellular with sheets of small round cells with staghorn vascular tree
  - Round cell component may not be prominent
- Mitotic activity, necrosis, and calcification common
- Central region merges with periphery composed of fascicles of plump spindle cells
  - Contain blunt-ended nuclei and eosinophilic cytoplasm
  - Resemble smooth muscle cells

## ANCILLARY TESTS

### Immunohistochemistry

- Spindle cells show myofibroblastic differentiation
- Both spindle-shaped cells and more round cell component are positive for vimentin and SMA
  - Spindle cells are negative for CD34

### Electron Microscopy

- Cells show myofibroblastic differentiation
  - Contain dilated rough endoplasmic reticulum, peripheral filaments with densities, and basal lamina

## DIFFERENTIAL DIAGNOSIS

### Low-Grade Fibroblastic Sarcoma

- More cellular than myofibroma
- More cytologic atypia
- Demonstrates infiltrative growth pattern

### Fibrous Dysplasia

- Typical curvilinear woven absent in myofibroma

### Desmoplastic Fibroma

- Neoplastic cells are spindled and arranged in broad fascicles: No round cells
- Staghorn vascular pattern absent

### Eosinophilic Granuloma and Nonossifying Fibroma

- Both enter into differential diagnosis radiographically but are easy to distinguish pathologically

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Think myofibroma for benign spindle cell tumor in infant

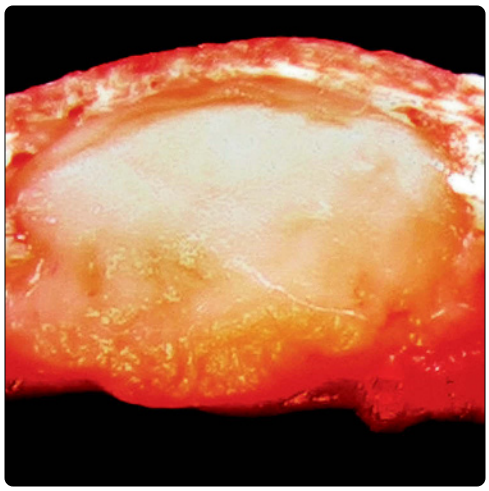
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**Solid Tan Tumor**

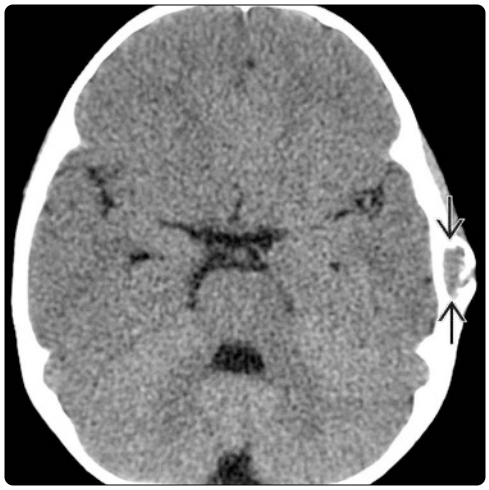


**Tumor in Diploic Space**



**(Left)** *This gross photograph of an intraosseous myofibroma shows that the tumor is well demarcated and has a tan-gray and yellow cut surface.* **(Right)** *Axial CT of an intraosseous myofibroma shows a well-defined lytic lesion arising in the occipital bone of the skull. Mild expansion of the bone is present, but the tumor is surrounded by sclerotic bone.*

**Small Myofibroma of Skull**

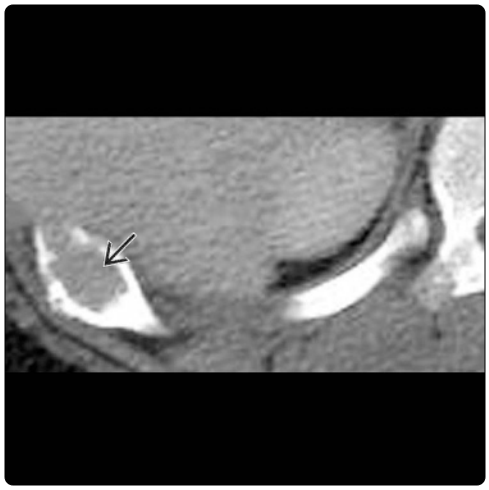


**Pathological Fracture**



**(Left)** *Axial CT shows a lytic lesion arising in the left parietal bone, very similar in appearance to the lesion in the previous image. The tumor is well defined, exhibits no calcifications, and has caused slight expansion of the outer table.* **(Right)** *Plain radiograph shows a monostotic myofibroma arising in the proximal radius. The lesion is lucent with fairly well-defined margins. A healing pathologic fracture is seen.*

**Tumor Expanding Rib**



**Multiple Myofibromas**

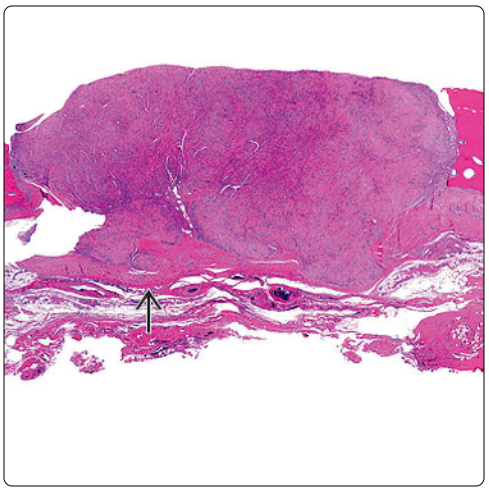


**(Left)** *Axial CT scan shows a single intraosseous myofibroma involving the rib. The lesion is lytic, ovoid in shape, and well demarcated.* **(Right)** *Plain radiograph of an infant with myofibromatosis demonstrates multiple lytic lesions involving the metaphyses of long tubular bones. Each individual lesion is lytic, oval in shape, and well demarcated. The findings are consistent with myofibromatosis.*

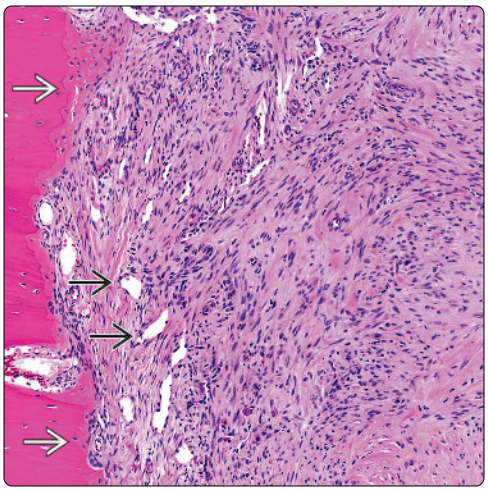


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### Well-Circumscribed Margins

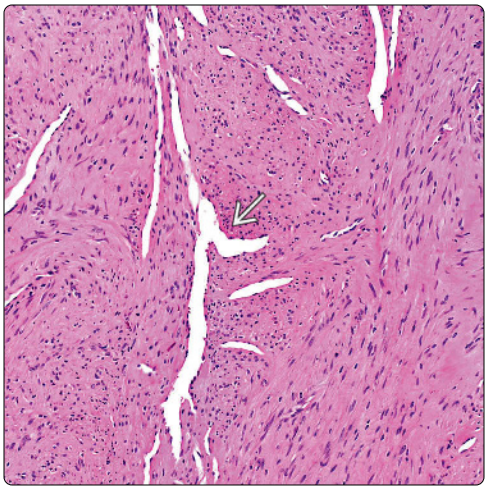


### Fascicles of Spindle Cells

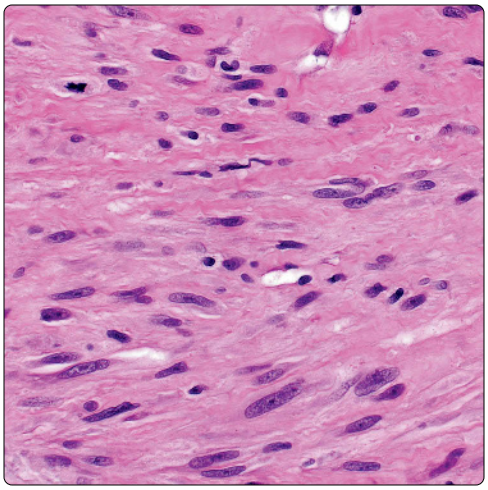


**(Left)** *Whole-mount section of an intraosseous myofibroma shows a well-demarcated tumor that has replaced the bone and extended into adjacent soft tissues, where it is surrounded by a layer of periosteum ⇨.* **(Right)** *Medium-power view of an intraosseous myofibroma shows bland-looking, spindle-shaped cells with eosinophilic cytoplasm. The spindle cells are arranged in fascicles. There are numerous blood vessels ⇨, and the tumor is well demarcated from the adjacent cortical bone ➡.*

### Staghorn Vascular Pattern

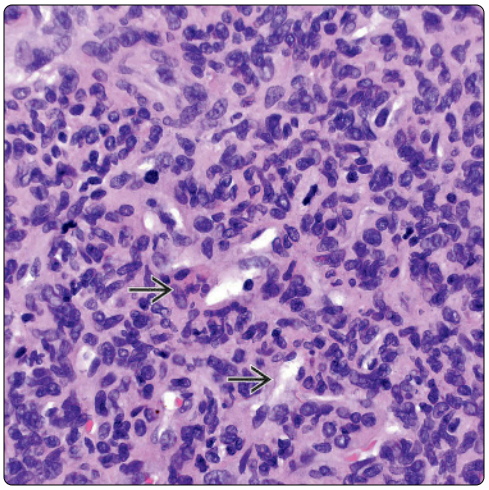


### Bland Spindle Cells

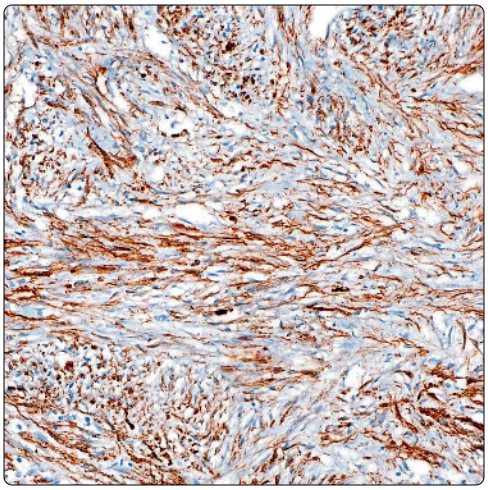


**(Left)** *In this intraosseous myofibroma, the neoplastic cells have a fascicular growth pattern, eosinophilic cytoplasm, and spindle-shaped nuclei. The vascular pattern is prominent, and some of the vessels have a branching, hemangiopericytoma-like configuration ➡.* **(Right)** *High-power view shows that the neoplastic cells are spindle-shaped with rounded nuclei, some of which have small nucleoli. The cytoplasm is pale pink, suggesting the presence of numerous intracytoplasmic filaments, suggestive of myogenic differentiation.*

### Round Cells



### Tumor Cells Positive for SMA



**(Left)** *The central region of myofibroma can be composed of sheets of round cells that are mitotically active. These areas can undergo necrosis and dystrophic calcification. The branching staghorn vessels are present in this tumor ⇨.* **(Right)** *An intraosseous myofibroma stained immunohistochemically for SMA shows diffuse cytoplasmic staining of the neoplastic cells.*



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KEY FACTS

## TERMINOLOGY

- Fibrosarcoma
- Collagen-producing fibroblastic and myofibroblastic sarcoma

## CLINICAL ISSUES

- Affects middle-aged and elderly adults
- Develops in irradiated bone or in background of Paget disease and bone infarction
- Pain
- Treated like osteosarcoma of bone
- 5-year survival rate ~ 60%

## IMAGING

- Destructive
- Poorly circumscribed
- Nonmineralized

## MICROSCOPIC

- High-grade tumor showing fibroblastic and myofibroblastic differentiation
- Composed of fascicles of pleomorphic spindle cells frequently arranged in herringbone or storiform pattern
- Multinucleated tumor giant cells, necrosis, and high mitotic rate often present
- Neoplastic cells often embedded within collagen-rich stroma

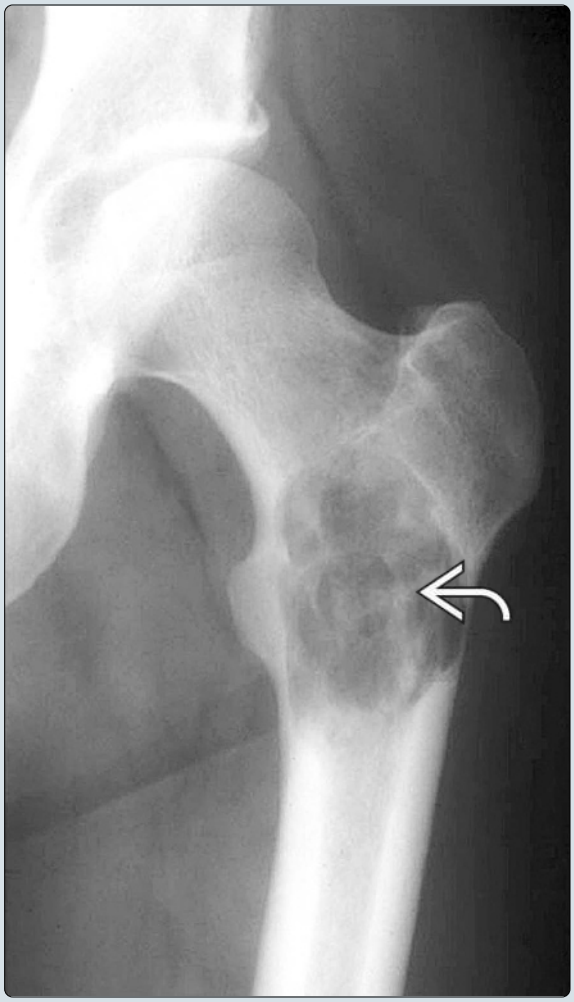
## ANCILLARY TESTS

- Immunohistochemical findings in fibrosarcomas are nonspecific but can be helpful in excluding other tumors in differential diagnosis

## DIAGNOSTIC CHECKLIST

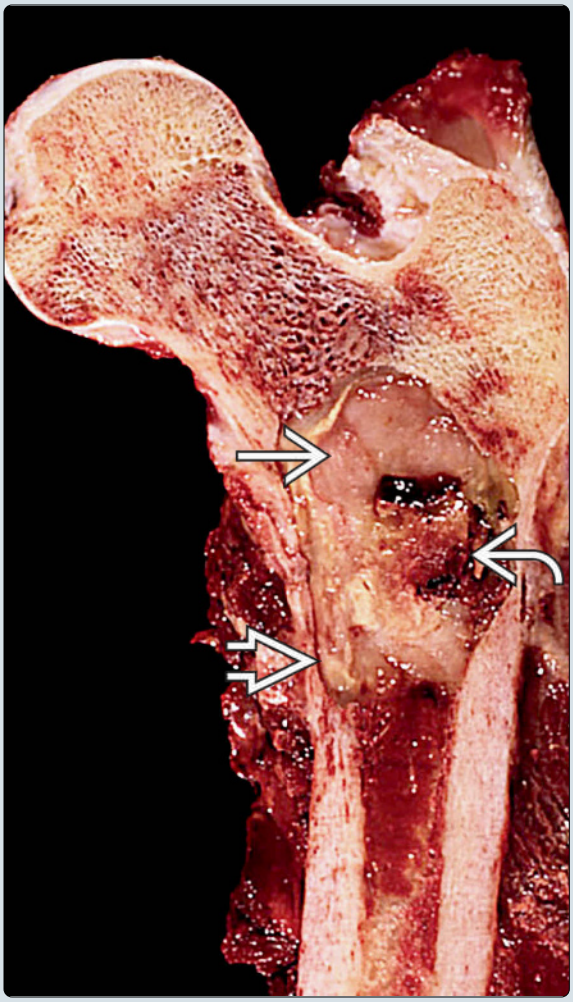
- Always look for underlying preexisting lesion, both histologically and radiographically, when encountering high-grade fibrosarcoma arising in bone

**Lytic Oval Tumor**



*AP radiograph of the proximal femur shows a metaphyseal lytic fibrosarcoma. The lesion contains internal calcifications, and it is impossible to distinguish between retained sequestra and neoplastic bone formation in this case. There is no significant periosteal reaction.*

**Hemorrhagic Tan Mass**



*Resected fibrosarcoma of the proximal femoral diaphysis is pink-tan with an area of hemorrhagic necrosis. The surrounding cortex is scalloped and thinned by the mass, which appears well circumscribed.*



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## TERMINOLOGY

### Synonyms

- Pleomorphic malignant fibrous histiocytoma
- High-grade fibrosarcoma
- Undifferentiated pleomorphic sarcoma
- Malignant fibrous xanthoma

### Definitions

- High-grade sarcoma showing fibroblastic &/or myofibroblastic differentiation
- Sarcomas without collagen production or immunohistochemical evidence of myofibroblastic differentiation are called undifferentiated pleomorphic sarcomas (UPS)

## ETIOLOGY/PATHOGENESIS

### Neoplastic

- Most tumors idiopathic with no known predisposing factor
- ~ 20% of fibrosarcomas of bone arise in preexisting condition (secondary UPS)
  - Paget disease
  - Patients with history of radiation to bone
  - Bone infarct
  - Diaphyseal medullary stenosis
- Can also arise in association with prosthetic devices

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Rare tumor
  - ~ 2% of primary malignant bone tumors
- Age
  - Wide age group but usually affects middle-aged and elderly individuals
  - Most patients are > 50 years at time of diagnosis
  - Rare cases occur in young individuals

### Site

- Long bones
  - Most commonly femur followed by tibia and pelvis
  - Usually arises in metaphysis or diaphysis of long bones

### Presentation

- Pain
- Mass
- Pathologic fracture

### Treatment

- Treated like osteosarcoma of bone
  - Combination of chemotherapy and surgery ± radiation therapy

### Prognosis

- 5-year survival rate ~ 40-50%
- Lung most common site for distant metastases

## IMAGING

### Radiographic Findings

- Radiographic features are nonspecific and indicate aggressive malignant neoplasm
- Destructive
- Lytic mass with moth-eaten pattern of destruction
  - Small sequestered fragments of residual bone may be present
- Poorly circumscribed
- Generally no sclerotic margin
  - If present, it is incomplete
- Metaphyseal and usually eccentrically located
- Cortical breakthrough and soft tissue mass commonplace
- May be signs of preexisting lesion

### MR Findings

- Isointense to skeletal muscle on T1-weighted images
- May show evidence of underlying lesion

### CT Findings

- Similar to radiographic findings

### Bone Scan

- Hot on bone scan

## MACROSCOPIC

### General Features

- Variable gross appearance
- Can be tan-white with areas of hemorrhage and necrosis
- Involving medullary cavity and extending into adjacent soft tissue

### Size

- Usually large at time of diagnosis

## MICROSCOPIC

### Histologic Features

- Identical to soft tissue counterpart
  - Very diverse morphologic features with different patterns
  - Most common subtypes in bone are storiform pleomorphic type and giant cell-rich type
- Fascicles of pleomorphic, spindle-shaped cells arranged in fascicular or storiform/pinwheel growth pattern
- Multinucleated osteoclast-type giant cells are present in giant cell-rich type
- Necrosis and high mitotic rate, including presence of atypical mitotic figures, is common
- Neoplastic cells often embedded within collagen-rich stroma that may be hyalinized
  - Often difficult to differentiate hyalinized collagen stroma from osteoid
- Cells with epithelioid morphology, prominent vasculature with hemangiopericytoma-like growth pattern may also be present
- Myxoid change commonly seen in myxofibrosarcoma of soft tissue, which is much less frequently encountered among intraosseous tumors
- Rare cases of sclerosing epithelioid fibrosarcoma have been reported



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## ANCILLARY TESTS

### Immunohistochemistry

- Immunohistochemical findings in fibrosarcomas are nonspecific but are helpful in excluding other tumors in differential diagnosis
  - Neoplastic cells are diffusely positive for vimentin and may show focal staining for smooth muscle markers
    - Indicative of fibroblastic and myofibroblastic differentiation
  - Occasionally, tumor cells may show some keratin positivity, raising possibility of metastatic sarcomatoid carcinoma
- Neoplastic cells can also stain for histiocytic markers

### Electron Microscopy

- Ultrastructurally, neoplastic cells usually show fibroblastic differentiation containing abundant intracytoplasmic rough endoplasmic reticulum
  - Some cells may contain myofibroblastic differentiation with peripheral filaments and densities
  - Some cells contain intracytoplasmic lysosomes (fibrohistiocytes)

## DIFFERENTIAL DIAGNOSIS

### High-Grade Osteosarcoma

- Presence of extracellular collagen deposition in fibrosarcoma can sometimes be difficult to differentiate from neoplastic bone
- Any mineralization of collagen fibers is suggestive of bone formation
- Sometimes diagnosis of osteosarcoma does not become apparent until after resection when neoplastic bone is appreciated
- Fortunately, both high-grade fibrosarcoma of bone and osteosarcoma are treated with osteosarcoma protocol and show similar response to chemotherapy

### Dedifferentiated Chondrosarcoma

- Dedifferentiated component in dedifferentiated chondrosarcoma is usually composed of undifferentiated pleomorphic sarcoma
- Radiographic correlation is helpful in identifying underlying low-grade cartilaginous tumor

### Metastatic Sarcomatoid Carcinoma

- When high-grade fibrosarcoma is keratin positive, metastatic sarcomatoid carcinoma has to be excluded
- Presence of single bone lesion favors primary bone tumor
- In some cases, electron microscopy can be helpful

### Leiomyosarcoma

- High-grade leiomyosarcoma can have similar histologic features
  - Neoplastic cells in leiomyosarcoma usually have more abundant eosinophilic cytoplasm
    - Stain for muscle markers, such as desmin, muscle actin, and smooth muscle actin
    - Ultrastructurally, they show smooth muscle differentiation

### Malignant Lymphoma

- Can mimic fibrosarcoma radiographically
- Easy to differentiate by light microscopy

### Angiosarcoma

- Usually lytic and highly aggressive radiographically
- Easy to distinguish histologically
  - Angiosarcoma stains for endothelial markers, which are negative in fibrosarcomas

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Always look for underlying preexisting lesion, both histologically and radiographically, when encountering high-grade fibrosarcoma arising in bone

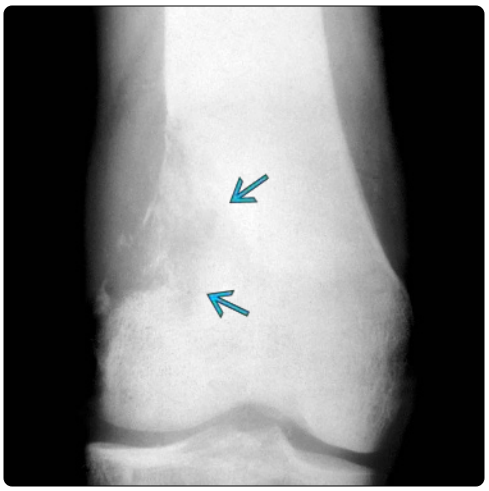
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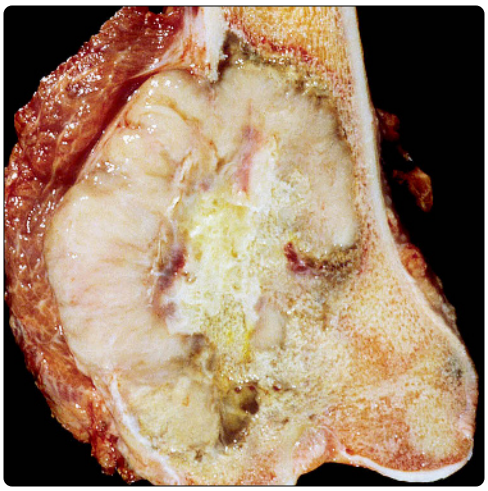



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### Eccentric Lytic Mass



### Solid and Focally Necrotic Mass

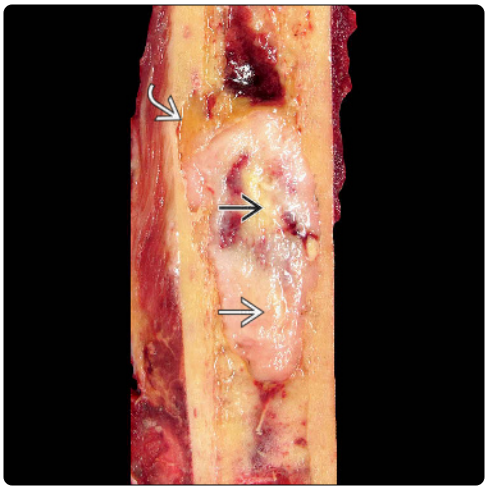


**(Left)** *AP radiograph of the distal femur reveals an eccentric lytic lesion ⇨ of the metaphysis. It contains small fragments of residual bone engulfed by the tumor (sequestra). The margins are "moth-eaten."* **(Right)** *High-grade fibrosarcoma of the distal femur appears as a variegated tan, fleshy mass with pale yellow areas of necrosis and foci of hemorrhage. The tumor destroys the cortex and extends into the soft tissues.*

### Moth-Eaten Diaphyseal Tumor

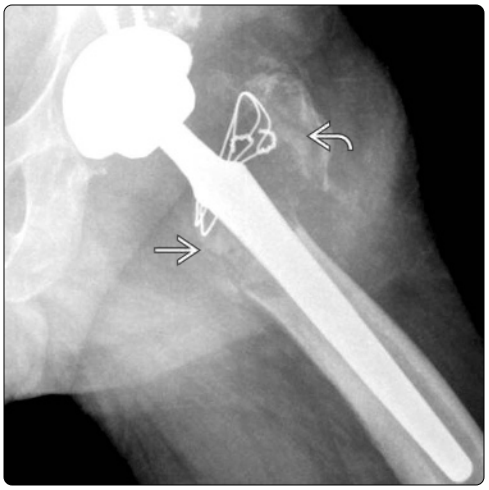


### Solid, Pink-Tan Mass

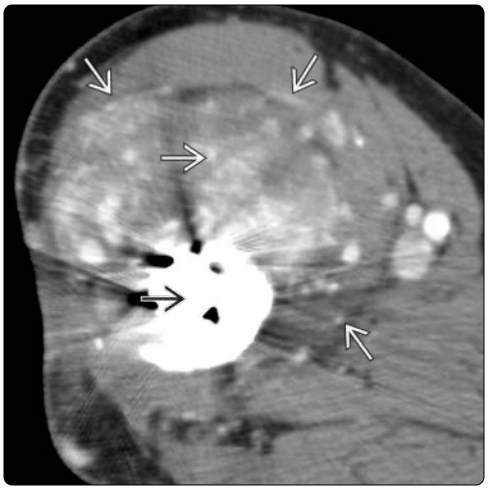


**(Left)** *A relatively uncommon diaphyseal presentation of a fibrosarcoma is shown. The lesion ➡ is lytic and destructive and also demonstrates the moth-eaten pattern of bone destruction consisting of small but macroscopic "holes" with preserved intervening bone.* **(Right)** *Resected fibrosarcoma of the femoral diaphysis appears as a solid, pink-tan mass ➡ with foci of hemorrhage. The central yellow region ⇨ represents necrosis. The tumor has eroded into the cortex ➡.*

### Destructive UPS Adjacent to Prosthesis



### UPS Arising in Prosthesis



**(Left)** *AP radiograph of the hip in frog lateral position shows a lytic, destructive undifferentiated pleomorphic sarcoma (UPS) ➡ in the proximal metaphysis around the femoral component of a total hip replacement. A pathological fracture of the greater trochanter ➡ is present.* **(Right)** *Axial CT of a UPS reveals a very large lesion ➡ surrounding the hip implant ⇨. High-density areas within the lesion are due to the use of intravenous contrast and indicate prominent vascularity.*

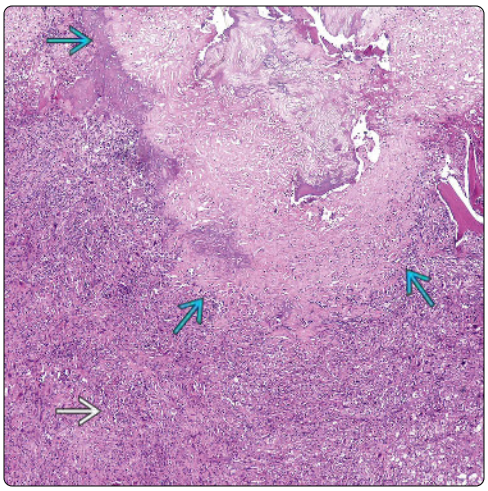


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### Treated Fibrosarcoma

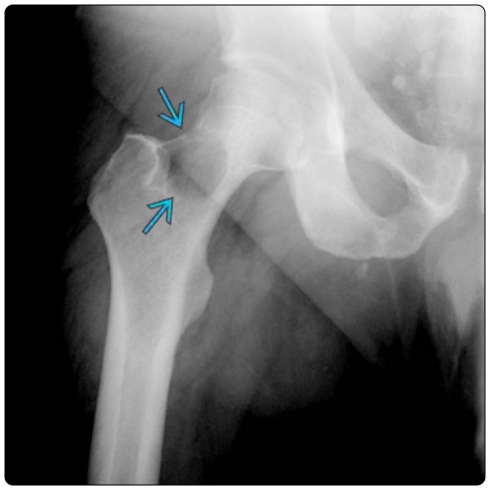


### Fibrosarcoma Arising in Bone Infarct

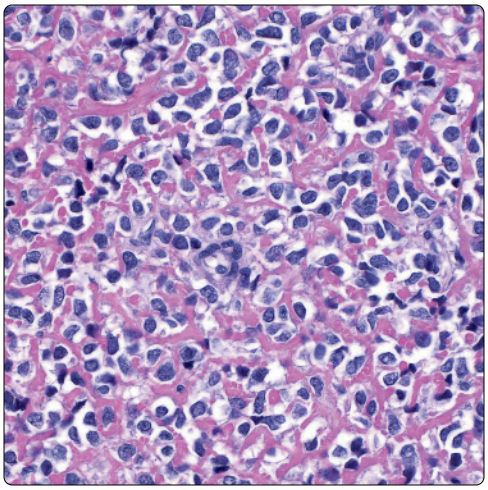


**(Left)** *High-grade fibrosarcoma of the distal femur after chemotherapy is shown. The tan and white portions of the tumor represent viable tumor, whereas the yellow regions are areas of necrosis.* **(Right)** *High-grade fibrosarcoma arising in association with a bone infarct is shown. The bone infarct is composed of necrotic bone and marrow that has been replaced with fibrous tissue. This area is juxtaposed to a high-grade fibrosarcoma.*

### Lytic, Circumscribed Tumor

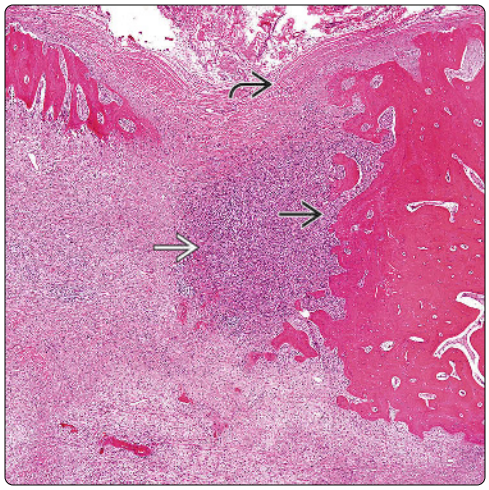


### Tumor Cells Surrounded by Collagen

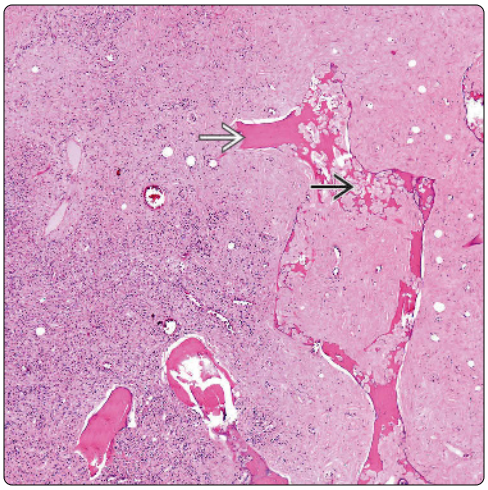


**(Left)** *Sclerosing epithelioid fibrosarcoma of bone arising in femoral neck is shown. The lesion is lytic and appears to be well demarcated. There is a possible small fracture on the lateral aspect of the cortex.* **(Right)** *Sclerosing epithelioid fibrosarcoma of bone composed of epithelioid neoplastic cells embedded in a lace-like collagen deposition, mimicking neoplastic bone, is shown. No mineralization of the collagen was identified, and the cells were diffusely MUC4 positive supporting the diagnosis of sclerosing epithelioid fibrosarcoma.*

### Destruction of Cortex



### Moth-Eaten Resorption of Bone

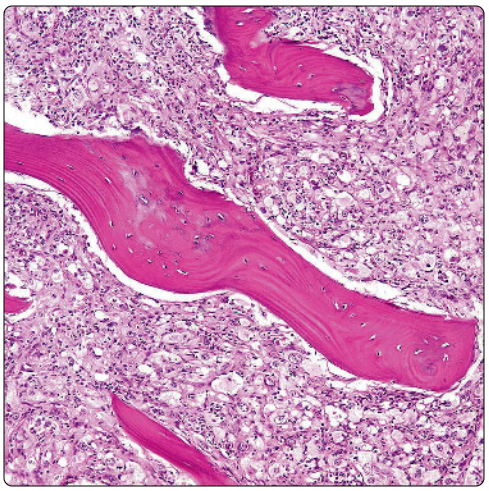


**(Left)** *Fibrosarcoma replaces the medullary canal and has resulted in focal destruction of the overlying cortex. The periosteum has not been transgressed. The tumor varies in cellularity with the darker regions representing hypercellular zones.* **(Right)** *Fibrosarcoma within the medullary canal has replaced the marrow fat and hematopoietic elements. It encases the preexisting cancellous bone and has resulted in irregular "moth-eaten" resorption of some of the bone.*

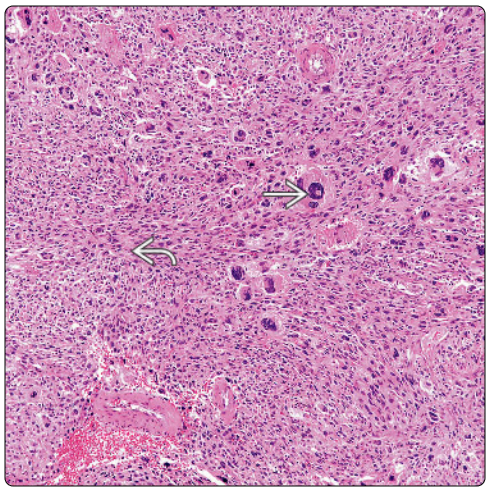


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### Permeative Growth Pattern

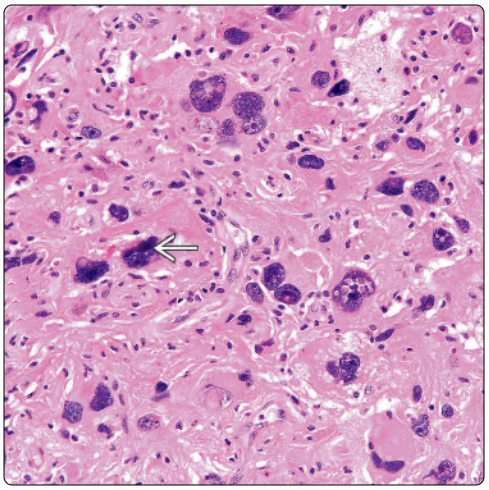


### Severe Nuclear Atypia

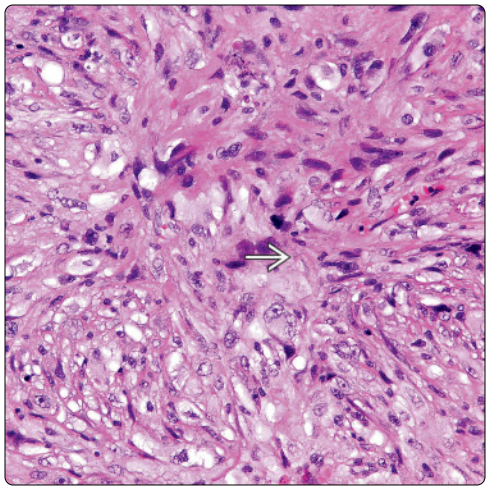


**(Left)** *Fibrosarcoma of bone permeates the medullary cavity and surrounds the bone trabeculae. This pattern correlates with a poorly defined margin on imaging studies. The tumor is composed of large pleomorphic polyhedral cells.* **(Right)** *Marked pleomorphism is a common finding in high-grade fibrosarcoma. The neoplastic cells can vary from spindle to epithelioid in shape. Some cells are giant and have extremely enlarged hyperchromatic nuclei. The spindle cells are arranged in fascicles.*

### Pleomorphism and Hyperchromasia

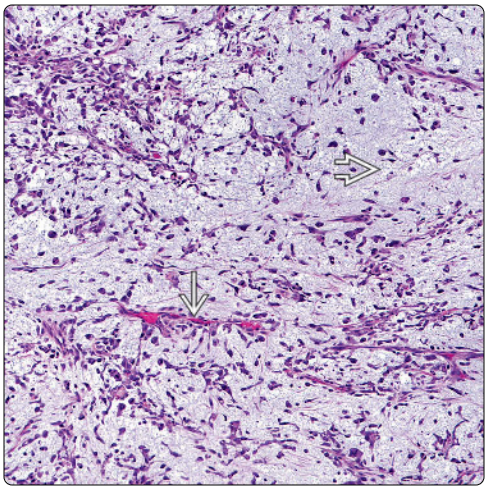


### Storiform Growth Pattern

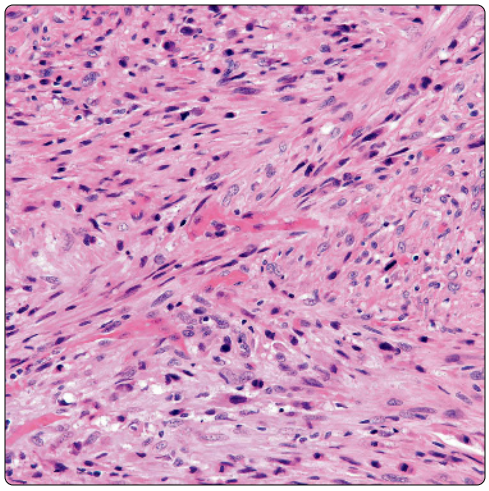


**(Left)** *High-grade fibrosarcoma that is composed of cells of varying sizes and shapes is shown. Often present are giant tumor cells with enlarged hyperchromatic nuclei and eosinophilic cytoplasm. Mitoses are often numerous, and foci of necrosis are commonplace.* **(Right)** *The tumor cells in fibrosarcoma are often arranged in fascicles, usually oriented in a storiform pattern. The fascicles radiate from a central area like spokes on a wheel.*

### Myxofibrosarcoma of Bone



### Myogenic Differentiation



**(Left)** *Minority of cases have abundant myxoid stroma similar to myxofibrosarcoma of soft tissue. In this variant, the spindle and stellate tumor cells float in a flocculent myxoid stroma with branching capillaries.* **(Right)** *Fibrosarcoma may be myofibroblastic in phenotype. Features of myofibroblastic differentiation include spindle cells with fibrillar eosinophilic cytoplasm and blunt-ended, spindle-shaped nuclei, supported by immunohistochemical stains for 1 or more myogenic markers*



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# Benign Fibrous Histiocytoma

KEY FACTS

## TERMINOLOGY

- Tumor composed of spindled, bland fibroblasts arranged in storiform pattern with scattered foamy macrophages and osteoclast-like giant cells

## CLINICAL ISSUES

- Uncommon tumor; most patients > 20 years old at time of diagnosis
- Long bones
- Curettage
- Local recurrence rate is very low

## IMAGING

- Radiolucent and well demarcated

## MACROSCOPIC

- Well circumscribed
- Tan to yellow to brown cut surface

## MICROSCOPIC

- Similar histologic appearance to benign fibrous histiocytoma (BFH) of soft tissue
- Admixture of spindle-shaped cells and foamy (xanthoma) cells
- Spindle-shaped cells are bland and arranged in storiform growth pattern
- When xanthoma cells predominate, diagnostic term xanthoma may be used
- Areas of necrosis may be seen in setting of pathologic fracture

## TOP DIFFERENTIAL DIAGNOSES

- Nonossifying fibroma
  - Distinction made clinically
- Giant cell tumor of bone
  - Syncytial growth of mononuclear cells whose nuclei are identical to those in osteoclast-like giant cells

**Lytic, Well-Circumscribed Mass**

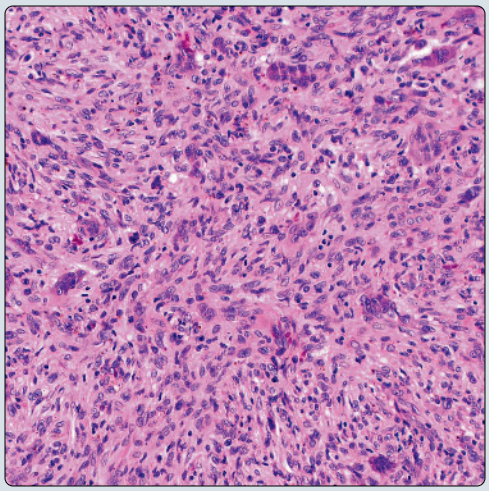


**Lytic, Well-Circumscribed Mass**

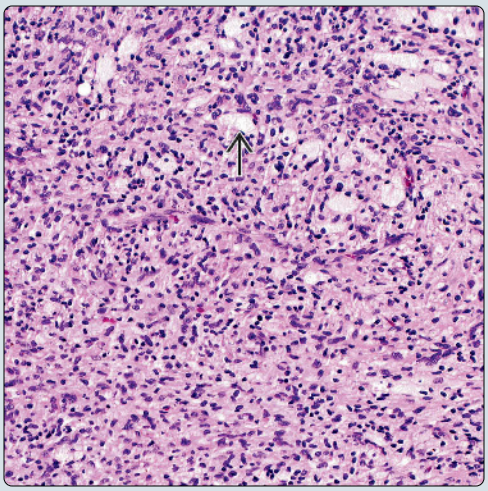


**(Left)** *Radiograph of benign fibrous histiocytoma of the distal femur shows an eccentric lytic mass that involves the metaphysis and a portion of the epiphysis. The tumor has well-circumscribed and sclerotic margins.* **(Right)** *The benign fibrous histiocytoma is present in the posterior ilium adjacent to the sacroiliac joint. The tumor has the same density as skeletal muscle and is well circumscribed with a sclerotic margin.*

**Spindle Cells in Storiform Pattern**



**Foamy Macrophages**



**(Left)** *Benign fibrous histiocytoma is a cellular neoplasm and composed of spindle cells arranged in short intersecting fascicles that often form a storiform pattern. Scattered throughout the tumor are osteoclast-like giant cells.* **(Right)** *Benign fibrous histiocytoma is composed of spindle cells arranged in a storiform pattern. Foamy histiocytes are often seen and sometimes are numerous.*



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## TERMINOLOGY

### Abbreviations

- Benign fibrous histiocytoma (BFH)

### Synonyms

- Fibroxanthoma
- Fibrous xanthoma
- Xanthofibroma
- Xanthogranuloma

### Definitions

- Tumor composed of spindled, bland fibroblasts arranged in storiform pattern with scattered foamy macrophages and osteoclast-like giant cells
- Morphologically identical to nonossifying fibroma and fibrohistiocytic areas frequently found in periphery of giant cell tumor of bone

## ETIOLOGY/PATHOGENESIS

### Developmental Anomaly

- Controversial whether fibrous histiocytoma of bone is distinct bone tumor or secondary phenomenon seen in preexisting primary bone tumor, such as nonossifying fibroma or giant cell tumor

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Uncommon tumor; incidence unknown
- Age
  - Affects all age groups
    - Most patients > 20 years old at time of diagnosis
- Sex
  - Slightly more common in females

### Site

- Long bones
  - Most commonly femur and tibia
    - Metaphyseal-epiphyseal, followed by diaphysis
- Pelvic bones
  - Most commonly ilium
- Ribs

### Presentation

- Pain, sometimes of long duration
- May be asymptomatic and discovered incidentally
- Rarely presents with pathologic fracture

### Treatment

- Curettage
- Resection when involving bone such as fibula

### Prognosis

- Local recurrence rate is very low

## IMAGING

### Radiographic Findings

- Radiolucent with no matrix production
- Well delineated
- Contains sclerotic margins

## MACROSCOPIC

### General Features

- Intramedullary
- Well circumscribed
- Tan to yellow to brown cut surface
  - Yellow areas are due to presence of foamy histiocytes
  - Brown areas are caused by hemosiderin deposition

## MICROSCOPIC

### Histologic Features

- Similar histologic appearance to BFH of soft tissue
- Admixture of spindle-shaped cells and foamy (xanthoma) cells
- Spindle-shaped cells are bland and arranged in storiform growth pattern
- Scattered osteoclast-like giant cells may be present
- Xanthoma cells have clear vacuolated cytoplasms due to abundant intracytoplasmic lipid
  - Found admixed with spindle-shaped cells, forming small clusters
- Scattered inflammatory cells may be present
- Areas of hemorrhage and hemosiderin deposition common
- When xanthoma cells predominate, diagnostic term xanthoma may be used
- Areas of necrosis may be seen in setting of pathologic fracture

## DIFFERENTIAL DIAGNOSIS

### Nonossifying Fibroma

- Histologically, BFH can be identical to nonossifying fibroma
- Distinction made clinically
  - Nonossifying fibroma is eccentrically located in long bones
    - Eccentric in metaphysis
    - Affects children and adolescents
  - BFH is nonmetaphyseal and usually in older individuals

### Giant Cell Tumor of Bone

- Giant cell tumor of bone is epiphyseal-metaphyseal
- Syncytial growth of mononuclear cells whose nuclei are identical to those in osteoclast-like giant cells
- Often has spindle cell areas identical to BFH

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- When encountering lesion that looks like nonossifying fibroma in unusual location, think BFH

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KEY FACTS

## TERMINOLOGY

- Mesenchymal neoplasm composed of oval to spindle-shaped cells with prominent branching (hemangiopericytoma-like) vascular pattern
- Most previously diagnosed hemangiopericytomas of bone are now classified as solitary fibrous tumors
- Primary hemangiopericytoma of bone probably does not exist and is nonspecific growth pattern rather than distinct entity

## CLINICAL ISSUES

- Most common location: Spine

## IMAGING

- Osteolytic

## MICROSCOPIC

- Patternless architecture
- Thick, "ropy" collagen bands

## ANCILLARY TESTS

- CD34 positive
- STAT6 has recently been shown to be sensitive and specific marker for solitary fibrous tumor

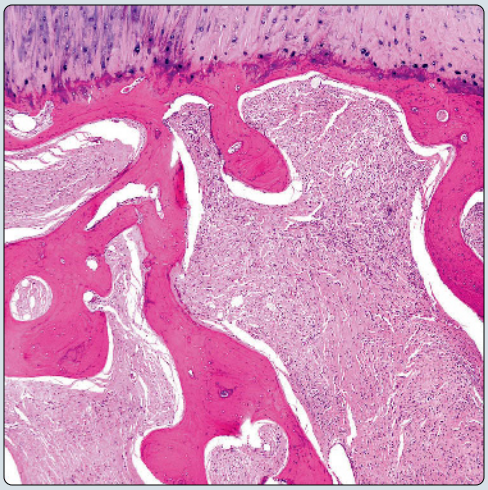
## TOP DIFFERENTIAL DIAGNOSES

- Synovial sarcoma
  - Can sometimes have very similar histologic features to solitary fibrous tumor
- Metastatic hemangiopericytoma
  - Metastatic hemangiopericytoma from meninges should always be excluded
- Mesenchymal chondrosarcoma
  - Mesenchymal chondrosarcoma can have prominent hemangiopericytoma-like vascular pattern simulating solitary fibrous tumor
- Phosphaturic mesenchymal tumor
  - Can have areas showing prominent branching vascular pattern

**Solitary Fibrous Tumor of Vertebra**

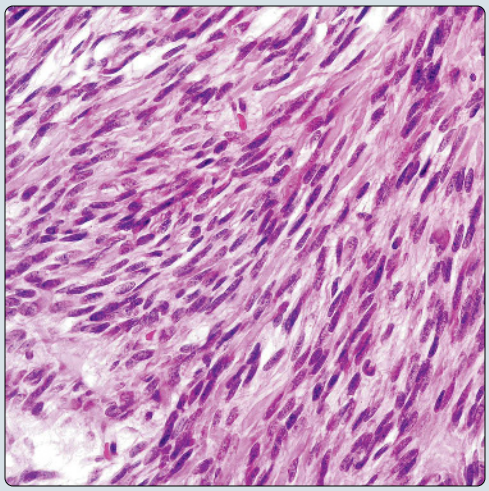


**Infiltrative Growth Pattern**

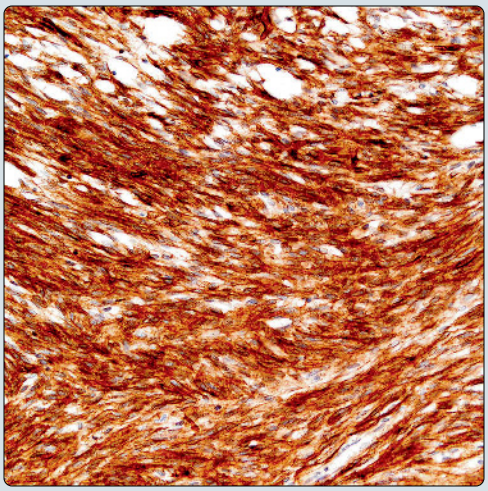


**(Left)** *Axial CT scan shows a mixed lytic and sclerotic lesion involving the body of a vertebra. The sclerotic rim suggests a nonaggressive lesion.* **(Right)** *Low-power H&E shows an intraosseous solitary fibrous tumor that diffusely infiltrates preexisting cancellous bone, including subchondral bone. The overlying articular surface is not involved.*

**Spindle-Shaped Cells**



**CD34**



**(Left)** *High-power view shows a solitary fibrous tumor. The neoplastic cells are arranged in short fascicles. Delicate bands of collagen separate neoplastic cells.* **(Right)** *A diffuse and strong positivity for CD34 is typical of solitary fibrous tumors. The tumor cells also stain for STAT6.*



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## TERMINOLOGY

### Definitions

- Mesenchymal neoplasm composed of oval to spindle-shaped cells with prominent branching staghorn vascular pattern, expression of CD34, and translocation
  - Term hemangiopericytoma no longer used
- Hemangiopericytoma of bone is not accepted diagnosis in WHO classification of soft tissue and bone tumors

## ETIOLOGY/PATHOGENESIS

### Genetic Aberration

- Solitary fibrous tumor was 1st described in pleura and was initially considered to be mesothelial in origin
- Specific genetic abnormality *NAB2-STAT6* gene fusion identified in majority of solitary fibrous tumor

## CLINICAL ISSUES

### Site

- Spine most common location
  - Usually sacrum or lumbar vertebrae
- Can develop in all organ systems

### Treatment

- Curettage or limited resection for benign tumors
- Malignant tumors are treated like other fibroblastic sarcomas of bone

### Prognosis

- Malignant tumors behave in aggressive manner and can metastasize

## IMAGING

### Radiographic Findings

- Osteolytic
- Moth-eaten pattern of bone destruction
- Soft tissue extension can be seen

## MACROSCOPIC

### General Features

- Firm, gray-white cut surface

## MICROSCOPIC

### Histologic Features

- Often patternless architecture
  - Characteristic thick, "ropy," keloidal-like collagen bands
- Variable cellularity with hypercellular and hypocellular areas
- Composed of oval to spindle-shaped fibroblast-like cells
  - Cells have uniform nuclei and small amount of pale eosinophilic cytoplasm
- Prominent branching, staghorn or hemangiopericytoma-like vascular pattern
  - Frequently, there is perivascular hyalinization
- Malignant tumors have increased cellularity, necrosis, infiltrative growth pattern, and increased mitotic activity (> 4 per 10 HPF)

## ANCILLARY TESTS

### Immunohistochemistry

- CD34 positive
  - Should be careful diagnosing solitary fibrous tumor if it is not CD34 positive
- STAT6 has recently been shown to be sensitive and specific marker for solitary fibrous tumor
- CD99 and Bcl-2 positive
- Focal cytoplasmic staining for epithelial membrane antigen and β-catenin
- Desmin, keratin, S100 protein negative

## DIFFERENTIAL DIAGNOSIS

### Synovial Sarcoma

- Can sometimes have very similar histologic features to solitary fibrous tumor
  - This can be problematic in monophasic synovial sarcoma but should be obvious in biphasic synovial sarcoma
- Synovial sarcomas are usually focally keratin positive
- In problematic cases, FISH for (X;18) translocation can be performed to confirm diagnosis of synovial sarcoma

### Metastatic Hemangiopericytoma

- Metastatic hemangiopericytoma from meninges should always be excluded
- More common than primary hemangiopericytoma of bone

### Mesenchymal Chondrosarcoma

- Mesenchymal chondrosarcoma can have prominent hemangiopericytoma-like vascular pattern simulating solitary fibrous tumor
- Unlike solitary fibrous tumor, mesenchymal chondrosarcoma is composed of round, ovoid, or spindle-shaped cells admixed with nodules of cellular hyaline cartilage
  - Cartilaginous differentiation is not present in solitary fibrous tumor

### Phosphaturic Mesenchymal Tumor

- Can have areas showing prominent branching vascular pattern
- Unlike solitary fibrous tumors, phosphaturic mesenchymal tumors frequently show matrix production (myxochondroid, osteoid-like) and flocculent mineralization
- Neoplastic cells in phosphaturic mesenchymal tumor express FGF23 but not CD34 immunohistochemically

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SECTION 6

# Fibroosseous Tumors




Fibrous Dysplasia **200**
Liposclerosing Myxofibrous Tumor **212**


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KEY FACTS

## TERMINOLOGY

- Common monostotic or polyostotic benign fibroosseous neoplasm of bone

## ETIOLOGY/PATHOGENESIS

- Mutation in cell surface G protein receptor results in constitutive activation and production of cyclic adenosine monophosphate (AMP) and hyperactivity of affected cells

## CLINICAL ISSUES

- Accounts for 7% of benign bone tumors
- Monostotic form 8-10x more common than polyostotic variant
- Bone lesions are often asymptomatic and discovered as incidental finding
- Bone pain most common symptom
- Polyostotic disease is associated with McCune-Albright and Mazabraud syndromes

## IMAGING

- Well-circumscribed tumor with ground-glass appearance; variable degree of radiolucency

## MACROSCOPIC

- Well circumscribed
- Solid or focally cystic, tan-white, gritty mass

## MICROSCOPIC

- Fibroosseous tumor: Woven bone trabeculae randomly arranged and curvilinear in configuration
- Bone appears to arise directly from fibrous tissue and demonstrates inconspicuous osteoblastic rimming
- Moderately cellular: Spindle cells are bland and arranged in storiform pattern

## TOP DIFFERENTIAL DIAGNOSES

- Well-differentiated osteosarcoma, desmoplastic fibroma, osteofibrous dysplasia, fracture callus, Paget disease, nonossifying fibroma

**Shepherd Crook Deformity**



**Large Fibrous Dysplasia**

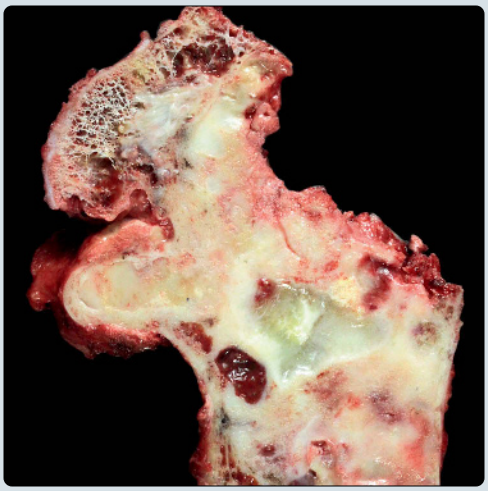


**(Left)** *AP radiograph shows a well-demarcated lesion with a ground-glass appearance involving the femur extending from the neck to the diaphysis and causing a marked varus or Shepherd crook deformity.* **(Right)** *A large fibrous dysplasia involving the diaphysis of the tibia is shown. The tumor is well circumscribed, solid, tan, and expands the bone, causing anterior bowing of the tibia.*

**Polyostotic Fibrous Dysplasia**



**Deformed Femoral Head**



**(Left)** *Polyostotic fibrous dysplasia causing marked deformity of the proximal femur is shown. The skeleton is replaced by ground-glass-appearing lesions involving the pelvic bones and the femur. A rod has been placed in the medullary cavity.* **(Right)** *Corresponding resection specimen demonstrated a marked deformed femoral head with flattening of the head and osteoarthritis. The medullary cavity is replaced by tan-white tissue that represents the fibrous dysplasia.*



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## TERMINOLOGY

### Abbreviations

- Fibrous dysplasia (FD)

### Definitions

- Common benign fibroosseous neoplasm of bone that may be solitary or multicentric
- FD associated with cutaneous café au lait spots and hyperactive endocrinopathy, especially precocious puberty, is known as McCune-Albright syndrome
  - Severity of manifestations in McCune-Albright syndrome depends on number and types of cells that harbor mutation in G protein
- FD associated with single or multiple soft tissue myxomas is known as Mazabraud syndrome

## ETIOLOGY/PATHOGENESIS

### Neoplasm

- Cytogenetic abnormalities have been described supporting neoplastic nature of FD
- All forms of FD are associated with nongerm cell mutation occurring during early embryogenesis
  - Missense mutation occurs at codon 201 within exon 8 of *GNAS* gene located on chromosome 20q; encodes α subunit of stimulatory G protein-coupled receptor, Gsα
  - Mutation results in arginine being replaced by either histidine (70%) or cysteine (30%)
  - G protein activation normally results in production of pathways that produce cyclic adenosine monophosphate (AMP)
  - Mutation in FD causes G protein receptor to be in state of constitutive activation so that excess cyclic AMP is produced
    - Melanocytes affected by mutation are hyperactive and produce increased amounts of melanin
    - Endocrine cells affected by mutation are hyperactive and secrete increased amounts of hormone
    - Osteoprogenitor cells affected by mutation proliferate, and their differentiation is limited so that tissue consists of spindle cells admixed with collagen fibers and woven bone trabeculae
- Involving gene coding for α subunit of cell surface guanine nucleotide binding receptor protein (G protein)
- Number and types of cells that harbor mutation in G protein determines severity of disease
- Mutation is acquired and not inherited

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - True incidence unknown as many lesions are asymptomatic
  - Accounts for ~ 5-7% of primary benign bone tumors; monostotic form is 8-10x more common than polyostotic form
  - McCune-Albright syndrome accounts for 2-3% of all cases of polyostotic FD
    - Prevalence of McCune-Albright syndrome is 1/100,000-1/1 million of population
  - Malignant transformation of FD is rare (< 1%) and is more common in patients with polyostotic disease or McCune-Albright syndrome
- Age
  - Bone lesions develop during childhood; many cases are diagnosed during early or mid adulthood
  - Polyostotic FD and McCune-Albright syndrome are usually diagnosed in childhood; 90% of skeletal lesions are present by 15 years
- Sex
  - No predilection

### Site

- Manifests as solitary monostotic (70-80%) or multiple monostotic or polyostotic (20-30%) lesions
  - May involve single bone, several bones, or many bones
  - In long bones, tumors are metadiaphyseal in location
- Solitary tumors usually arise in rib followed by femur, tibia, jaw bones, calvarium, and humerus
- Polyostotic tumors may be unilateral, involving 1 or more bones of extremity, or bilateral
- Polyostotic tumors arise in femur, followed by skull, tibia, humerus, ribs, fibula, radius, ulna, mandible, and vertebrae
  - Craniofacial involvement present in 50% of patients who have several bones affected and in 100% of patients with extensive skeletal disease
  - Polyostotic disease has propensity to affect pelvic and shoulder girdles
- Polyostotic lesions in McCune-Albright syndrome are often unilateral, and café au lait macules are usually limited to same side of body
  - Café au lait macules are commonly located on neck, chest, back, shoulder, and pelvic region

### Presentation

- Clinical presentation occurs in all age groups but most diagnosed by 4th decade
- Bone lesions are often asymptomatic and discovered as incidental finding
- Bone pain most common symptom
  - Limp and scoliosis less frequent
- Solitary lesions infrequently present as pathologic fracture
- Polyostotic disease may cause severe, sometimes crippling, deformities and recurrent fractures
  - Diffuse lesions in large weight-bearing bones are prone to bowing
    - Involvement of proximal femur produces Shepherd crook deformity
  - Most fractures involve proximal femur
  - Peak fracture rate in children 6-10 years of age
  - Limb length discrepancies common
- Craniofacial involvement may produce significant cosmetic disfigurement
  - Facial asymmetry, leontiasis ossea, exophthalmus, chronic headache
- McCune-Albright syndrome presents with complications of bone lesions and endocrinopathy
  - Precocious puberty most common
    - Affects girls much more often than boys
    - Associated with vaginal bleeding and premature development of breast tissue



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- Other endocrinopathies include hyperthyroidism, growth hormone excess, Cushing syndrome, and renal phosphate wasting

### Natural History

- Tumor(s) develops during formation and growth of skeleton
- Solitary lesions enlarge in proportion to growth of skeleton
- Lesions may or may not become quiescent in adulthood
  - Polyostotic lesions often continue to grow after skeletal maturity is attained
- Lesions may grow during pregnancy

### Treatment

- Depends on extent and severity of disease
- Therapy ranges from observation to surgical removal, usually in form of curettage
  - Asymptomatic lesions with no risk of fracture or deformity can be observed
  - Surgery may be required for correction of deformity, prevention or repair of pathologic fracture, and removal of symptomatic tumor
- Medical treatment of patients with polyostotic disease with bisphosphonates has yielded promising results regarding control of bone pain and slowing growth of tumors

### Prognosis

- Depends on extent and severity of disease
  - Excellent prognosis for asymptomatic disease or lesions amenable to treatment
  - Lesions that are symptomatic, located in critical areas, and difficult to remove may cause significant disability
    - Unremitting pain, recurrent fractures, severe deformity
- Bone lesion may undergo malignant transformation
  - Complication of solitary and polyostotic tumors
  - Occurs years after initial diagnosis
  - Often develops in tumors that have been previously radiated
  - Common sarcomas are osteosarcoma, fibrosarcoma, chondrosarcoma

### Other Clinical Findings

- Café au lait macules are most common extraskeletal manifestation of FD
  - Present in over 50% of patients with polyostotic FD
    - Borders of macules are irregular like coast of Maine and not as smooth as in neurofibromatosis
- Endocrine abnormalities in McCune-Albright syndrome may involve adrenal, pituitary, parathyroid, and thyroid glands
  - Hyperthyroidism 2nd most common endocrine abnormality
- May be associated with phosphate wasting and infrequently with oncogenic osteomalacia
  - Levels of FGF-23 are often elevated
- Compression neuropathies caused by bones expanded by tumors

## IMAGING

### Radiographic Findings

- Elongate intramedullary tumor
  - Tumors range from small (< 1 cm) to large (> 10 cm)
  - Often involves diaphysis and metadiaphysis
  - Epiphyseal involvement uncommon when growth plates are open
- Well-defined margins
  - Margin may be sclerotic and have rind-like appearance
    - Rind is sharply demarcated from surrounding bone
    - Proximally or distally, margin may be linear and triangular in configuration
- Lesions in craniofacial skeleton may be less defined as tumor blends with surrounding bone
- Tumors often result in expansive remodeling of bone
  - Rare lesions produce prominent eccentric expansion; such lesions are known as FD protuberans
- Classically produce ground-glass appearance; degree of radiolucency or density is variable
  - Amount of bone and its state of mineralization determine radiodensity of lesion
- Produce endosteal scalloping and thinning of cortex
- Do not elicit prominent periosteal reaction unless there has been fracture
- Tumors of femoral neck can cause marked varus or Shepherd crook deformity
- Areas of dense, punctate or flocculent radiodensities represent calcified cartilaginous component

### MR Findings

- Define extent, shape, and content of tumor
- T1 and T2 signal intensity determined by amount of fibrous tissue, cellularity, bone matrix, mineral, hemorrhage, and edema fluid
  - Many cases have low signal intensity on T1-weighted images, whereas T2-weighted images often show higher signal intensity
    - Cysts have high signal intensity on T2-weighted images due to high water content

### CT Findings

- Demonstrates extent of lesion
- Signal density of lesion depends on amount of bone and its state of mineralization
  - Fibrous component has low or soft tissue density
  - Mineralized bone component has high or bright density

### Bone Scan

- Markedly increased uptake in actively forming lesions
  - Increased uptake of lesion throughout life, but intensity diminishes as growth ceases

### PET Scan

- Lesions demonstrate increased uptake

## MACROSCOPIC

### General Features

- Centered in medullary cavity
  - May cause expansion of bone
    - Asymmetric expansion results in protuberant lesions
- Well circumscribed and surrounded by preexisting or reactive bone
  - Easily peels away from neighboring cortical and cancellous bone
  - Does not invade soft tissue



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- Solid or focally cystic
- Tan-white and gritty, rubbery or leather-like consistency
- Erodes and thins cortex
- In minority of instances, nodules of gray or pearly white cartilage are present

### Sections to Be Submitted

- Curettage specimen: Submit first 10 cassettes
- Resection specimen: Submit 1 section per centimeter of tumor, sample margins, and fracture site, if present

### Size

- Variable in size and can involve entire length of bone
  - Range from < 1 cm to > 10 cm in greatest dimension

## MICROSCOPIC

### Histologic Features

- Usually well delineated
- Composed of fibrous-appearing tissue and bone trabeculae
- Moderately cellular and spindle cells in fibrous-appearing tissue often arranged in storiform pattern
  - Spindle cells have bland, tapered nuclei and inconspicuous, eosinophilic cytoplasm
  - Mitotic activity very low
  - Sometimes stroma is edematous and fibromyxoid in appearance
  - Stroma contains multiple delicate capillaries
- Woven bone trabeculae are randomly arranged and irregular and curvilinear in configuration
  - Seldom contain cement lines
- Woven bone trabeculae are discontinuous, appear to arise directly from fibrous tissue, and demonstrate inconspicuous osteoblastic rimming
  - Osteoclasts may be numerous
  - Collagen fibers often extend directly from fibrous stroma into woven bone
  - Some tumors, especially those of craniofacial skeleton, may have abundant bone
- Some tumors show cystic change that can mimic aneurysmal bone cyst
  - Infrequently, bone has focal lamellar pattern
- Some areas of tumor may have very little bone
- Collections of foamy histiocytes mimicking xanthoma or fibroxanthoma may be present
- Cellular nodules of hyaline cartilage are present in ~ 20% of cases; these lesions have been known as fibrocartilaginous dysplasia
  - Cartilage may appear as disorganized growth plate-like cartilage
- Matrix resembling cementum may be found in lesions of craniofacial skeleton and less frequently in bones of extremities
- Necrosis may result from pathologic fracture

## ANCILLARY TESTS

### Immunohistochemistry

- No diagnostic immunophenotype
- Spindle cells express vimentin
- Spindle cells do not express keratin, EMA, MDM2, or CDK4

## DIFFERENTIAL DIAGNOSIS

### Well-Differentiated Osteosarcoma

- Most important tumor to exclude
- Imaging studies often reveal permeative margins and lack of sclerotic border
- Histologically grows with infiltrative pattern encasing preexisting lamellar bone trabeculae
- Tumor is more cellular than FD
- Tumor cells demonstrate greater cytologic atypia and occasional mitoses
- Tumor cells arranged in fascicles but not oriented in storiform pattern
- Karyotype reveals giant ring and marker chromosomes involving chromosomes 12q13-15
- Immunohistochemistry shows that tumor cells express MDM2 and CDK4

### Desmoplastic Fibroma

- Bone formation is not component of desmoplastic fibroma
- Spindle cells are arranged in broad, intersecting fascicles

### Osteofibrous Dysplasia

- Arises in anterior cortex of tibia followed by fibula
  - Epicenter of tumor is not medullary canal
- Tumor bone rimmed by prominent osteoblasts (not present in FD)
- Many spindle cells express keratin and EMA

### Fracture Callus

- Bone is deposited in purposeful fashion: Trabeculae often parallel to one another
- Bone rimmed by metabolically active osteoblasts

### Paget Disease

- Similar anatomic distribution as FD
- Diagnosed in older adult population
- Diagnostic findings are mosaic pattern of lamellar bone (not present in FD)
  - Pagetic bone has numerous cement lines
  - Active disease is characterized by numerous large osteoclasts and prominent osteoblastic rimming

### Nonossifying Fibroma

- Eccentric, metaphyseal, and radiolucent
- Hypercellular with spindle cells in storiform pattern with scattered multinucleated giant cells
- Lacks neoplastic bone

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Benign, well-circumscribed fibroosseous tumor
- Neoplastic bone is woven and lacks conspicuous osteoblastic rimming
- Moderately cellular tumor composed of spindle cells arranged in storiform pattern

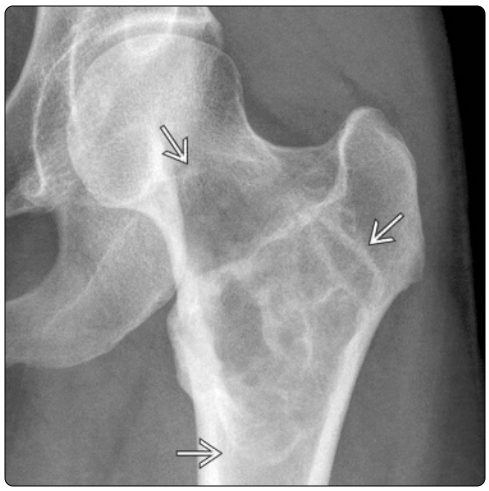
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1. Majoor BC et al: Outcome of long-term bisphosphonate therapy in McCune-Albright syndrome and polyostotic fibrous dysplasia. J Bone Miner Res. ePub, 2016



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Lucent and Sclerotic Lesion

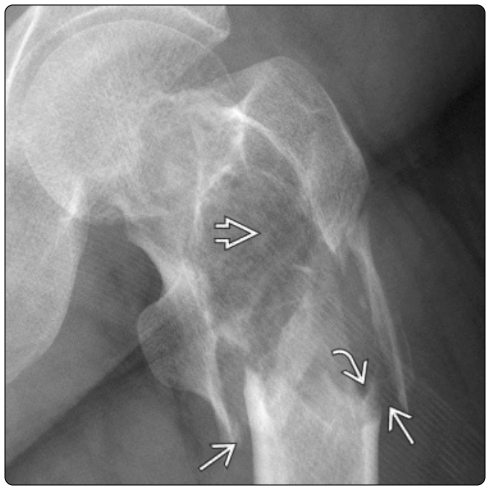


Lucent Lesion



**(Left)** *Typical example of fibrous dysplasia in the proximal femur is shown manifesting as a mixed lucent and sclerotic lesion with well-defined sclerotic margins and the characteristic involuting margin fading into the lesion on the inside and smooth on the outside.* **(Right)** *Coronal CT reformatted image of fibrous dysplasia shows a lucent lesion with no internal matrix. The margins are well defined and have an undulating contour with septa extending into the lesion.*

Lytic Tumor



Pathologic Fracture

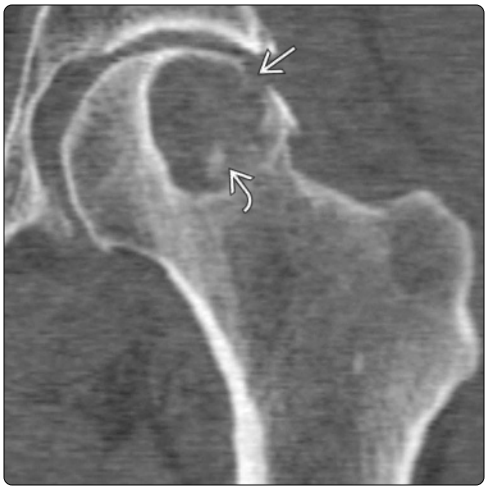


**(Left)** *Monostotic fibrous dysplasia of the proximal femur shows a pathologic fracture through its distal component. The lesion is largely lytic with subtle mineralization and has well-defined sclerotic margins; the distal margin has a scalloped contour.* **(Right)** *Coronal T1W1 MR with gadolinium and fat saturation shows a heterogeneous enhanced fibrous dysplasia of the proximal femur with nonenhancing hypointense signal at the fracture site.*

Well-Demarcated Lesion



Small Fracture

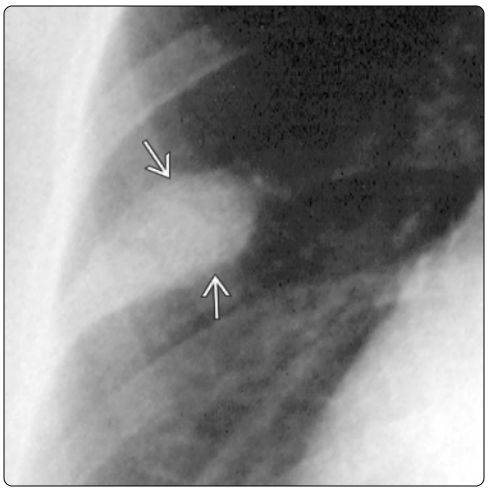


**(Left)** *Fibrous dysplasia of the femoral head with a well-delineated sclerotic margin is shown. The tumor has a hazy ground-glass internal density.* **(Right)** *Coronal CT scan of fibrous dysplasia of the femoral head shows focal disruption along the lateral articular surface. A fallen fragment suggests that the tumor may have a cystic component. The surrounding margins are sclerotic, typical of fibrous dysplasia.*

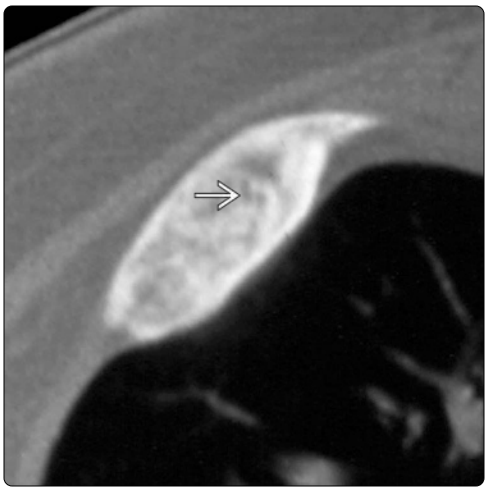


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### Fibrous Dysplasia of Rib

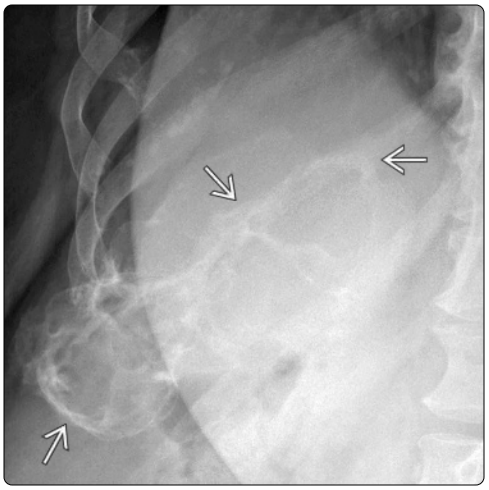


### Fibrous Dysplasia With Chondroid Areas



**(Left)** *Fibrous dysplasia of the rib is shown in a common location for this tumor. The intraosseous mass is elliptical, sharply defined, and has a homogeneous, ground-glass appearance. The lesion has caused expansion of the bone.* **(Right)** *Axial CT scan through fibrous dysplasia of the rib shows an intraosseous, expanded lesion with internal matrix densities. The round, nodular radiolucencies suggest that there may be a cartilaginous component in addition to the bone.*

### Bubbly, Lobulated Mass



### Expansile Mass of Rib



**(Left)** *Fibrous dysplasia involving almost the entire rib presents as a large, bubbly, lobulated, and expanded mass . The lesion expands the bone and scallops and attenuates the newly formed cortex.* **(Right)** *Coronal CT scan of fibrous dysplasia of the rib shows an expanding mass with heterogeneous internal densities . The thickened, rind-like cortex shows focal attenuation, which may represent an actively growing component of the tumor. Note the pressure effect on the liver.*

### Fibrous Dysplasia Protuberans



### Fibrous Dysplasia Protuberans



**(Left)** *Axial CT scan of fibrous dysplasia protuberans of the rib shows a large, pedunculated, heterogeneous mass arising from the posterolateral rib bulging into the pleural space. Note associated pleural effusion and a separate, expanded posterior rib lesion adjacent to the costotransverse joint.* **(Right)** *Coronal T1WI MR of fibrous dysplasia protuberans of the rib shows a large heterogeneous mass projecting into and compressing the left lung.*

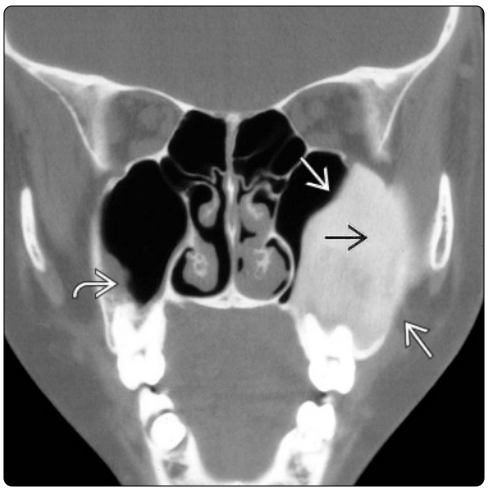


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### Classic Ground-Glass Appearance



### Ground-Glass Lesion of Maxilla



**(Left)** *Fibrous dysplasia of the mandible is shown that expands, scallops, and thins the cortex. The abundant lesional bone produces the characteristic ground-glass appearance. The margins are well defined and teeth are missing on the right.* **(Right)** *Fibrous dysplasia of the lateral maxilla is shown presenting as a homogeneous expanded mass with characteristic ground-glass density. The lesion bulges into the maxillary sinus. Mucoperiosteal thickening is noted in the right maxillary sinus.*

### Fibrous Dysplasia of Vertebral Body



### Lucent and Ground-Glass Appearance



**(Left)** *Lateral view of the cervical spine shows fibrous dysplasia expanding the C2 vertebral body and extending into and expanding the posterior elements. The tumor has a mixed lytic and ground-glass appearance.* **(Right)** *Sagittal CT scan of fibrous dysplasia of the vertebra shows a well-circumscribed mass that fills the medullary cavity, has a ground-glass appearance with focal lucencies, and expands the zygapophyseal articular facet of C2.*

### Well-Defined Mass of Diaphysis



### Hyperintense Lesion



**(Left)** *Fibrous dysplasia of the mid femoral diaphysis shows a well-defined mass that has a faint ground-glass appearance. The involved segment of femur is mildly expanded, and the cortex is scalloped and thinned anteriorly and posteriorly.* **(Right)** *Coronal T2WI MR with fat saturation of fibrous dysplasia of the femur shows the extent of the lesion. The proximal margin is oblique, and the cortex is scalloped. The tumor has a mostly uniform hyperintense signal.*



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### Cartilaginous Fibrous Dysplasia



### Fibrocartilaginous Dysplasia



**(Left)** *Fibrous dysplasia in the femoral neck and subtrochanteric region expands and deforms the bone. The distal 2/3 of the mass has a ground-glass appearance ⇒, and the proximal portion has oval radiolucencies suggesting a cartilaginous component ⇒.* **(Right)** *Sagittal T2WI MR of fibrous dysplasia with cartilage has a mostly hyperintense signal intensity ⇒. A small hypointense signal intensity in the center ⇒ may represent mineralized tumor bone.*

### Diffuse Fibrous Dysplasia

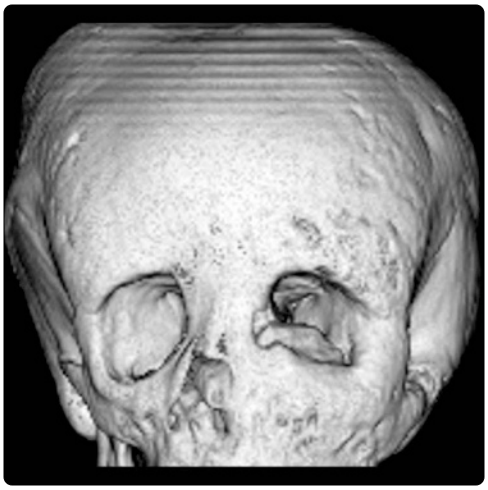


### Lucent and Sclerotic Lesion



**(Left)** *Diffuse involvement of the tibia by fibrous dysplasia causes expansion and deformity of the bone. Note the ground-glass matrix density and undulating contour of the inner aspect of the tibial cortex ⇨.* **(Right)** *A mixed lucent and sclerotic fibrous dysplasia involving the proximal radius ⇒ is shown. The tumor expands the bone, has well-defined margins, and causes pressure effect on the adjacent ulna. Another lesion ⇒ is present in the distal radial diaphysis.*

### Polyostotic Fibrous Dysplasia



### Polyostotic Fibrous Dysplasia of Skull



**(Left)** *3D reconstructed CT scan of polyostotic fibrous dysplasia of the skull shows deformity of the craniofacial bones. Bulging lesions from the frontal and zygomatic bones project into and deform the left orbit.* **(Right)** *Polyostotic fibrous dysplasia of the skull with a ground-glass appearance on CT is shown. The tumors cause diffuse expansion of the diploic space and obliteration of left mastoid air cells ⇨. There is also involvement of the base and lateral masses ⇒ of C1.*



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### Lytic and Trabeculated Tumor



### Prominent Ground-Glass Appearance

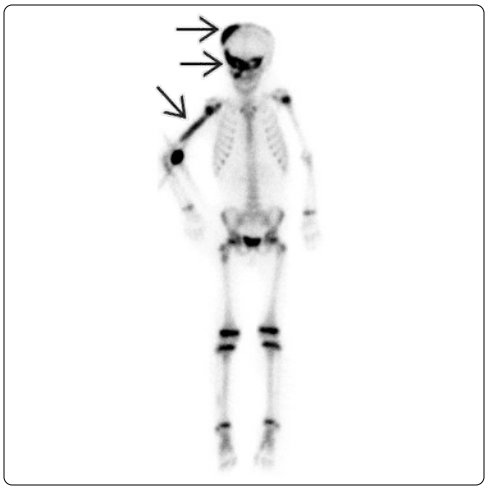


**(Left)** *Polyostotic fibrous dysplasia expands the entire humeral shaft. The tumor is lytic and trabeculated and thins the cortex. A healed fracture deforms the mid shaft ➡. The scapula is deformed by another lesion ⇨. (Right) Polyostotic fibrous dysplasia with a prominent ground-glass appearance expanding the proximal ulna is shown. The pressure effect on the adjacent radius suggests the slow growth of the lesion. A smaller tumor is present in the proximal radius ➡.*

### Shepherd Crook Deformity



### Hot on Bone Scan

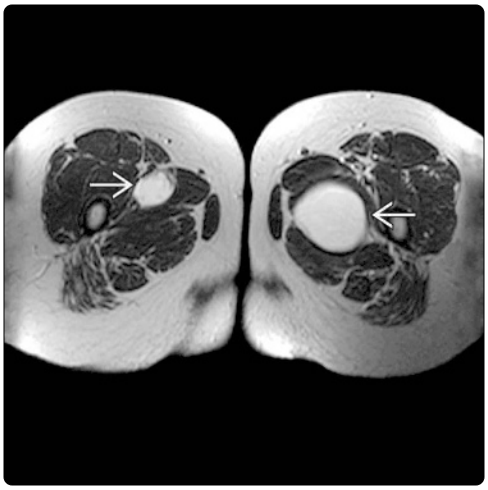


**(Left)** *Shepherd crook deformity of the proximal femur ➡ is caused by fibrous dysplasia. The tumor expands and deforms the femoral neck and intertrochanteric region. The acetabulum is distorted by the longstanding process. Plate, screws, and a fibular graft ⇨ from prior fixation are seen. Also, note the expansion of the distal shaft with significant cortical thinning. (Right) Technetium-99m scan shows sites of fibrous dysplasia with dense uptake ⇨ of the radionucleotide.*

### Café Au Lait Lesion



### Mazabraud Syndrome

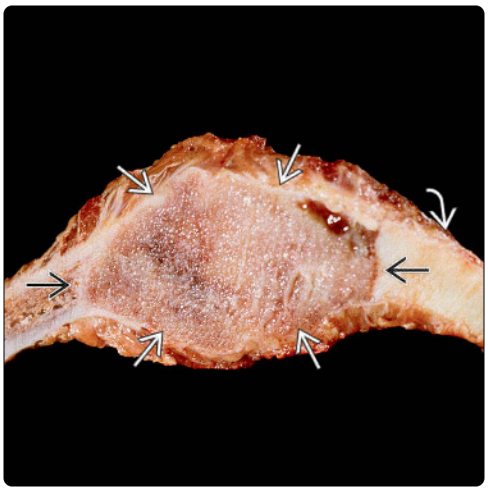


**(Left)** *Characteristic café au lait cutaneous pigmented lesion in a patient with fibrous dysplasia is shown. The brown macule produced by hyperfunctioning melanocytes has typical irregular margins. (Right) Axial T2WI MR of a patient with polyostotic fibrous dysplasia and intramuscular myxomas ➡ (Mazabraud syndrome) shows that the myxomas are oval or round, well circumscribed, < 5 cm in diameter, and hyperintense. The adjacent femurs are unremarkable.*

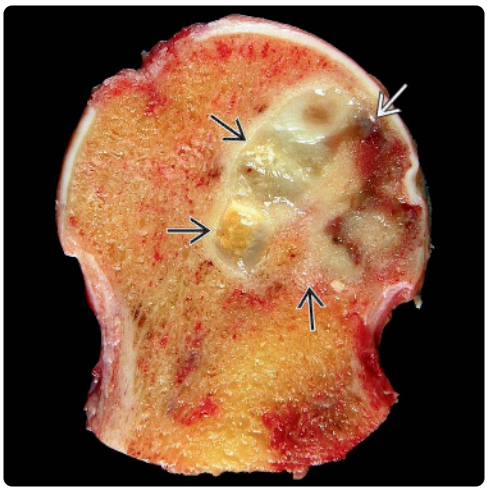


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### Solid, Tan-Brown Tumor of Rib

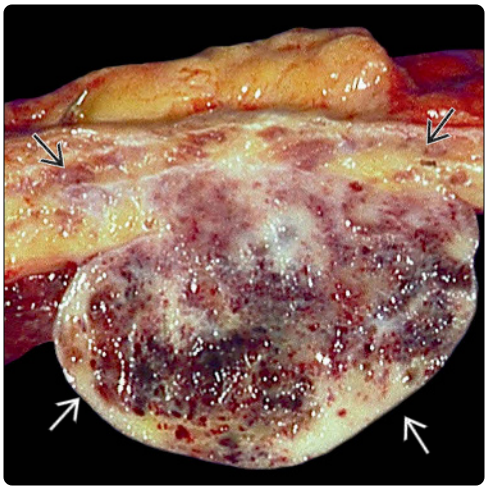


### Well-Defined, Yellow-Tan-White Lesion



**(Left)** *Fibrous dysplasia is shown arising in a rib, which is a common site for the lesion. The solid, tan-brown tumor expands the rib and is delineated and confined by a thin rim of subperiosteal* ➡ *and intramedullary reactive bone* ⇨*. Costal cartilage* ➡ *abuts one end of the tumor.* **(Right)** *Fibrous dysplasia of the femoral head, which extends to the subchondral bone plate* ➡*, is shown. The tumor is well demarcated from the surrounding trabecular bone* ⇨ *and has a glistening, yellow-tan-white cut surface.*

### Fibrous Dysplasia Protuberans

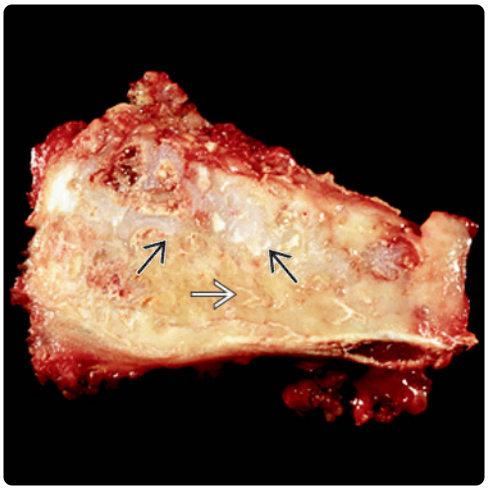


### Cystic Fibrous Dysplasia

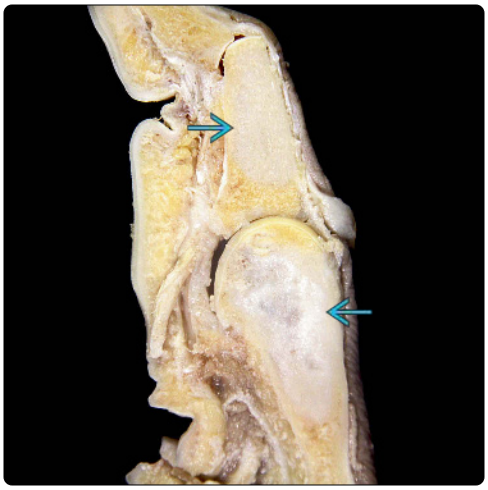


**(Left)** *Fibrous dysplasia protuberans of the rib is shown arising in the medullary cavity* ⇨ *and expanding the cortex to form a large, protuberant mass* ➡*. The cut surface is variegated, tan, gray, and brown with small hemorrhagic cystic areas.* **(Right)** *Multicystic fibrous dysplasia expanding and distorting the underlying bone is shown. The tumor is tan-white and contains large, oval cysts that are surrounded by solid portions of the mass.*

### Fibrous Dysplasia With Cartilage



### Polyostotic Fibrous Dysplasia

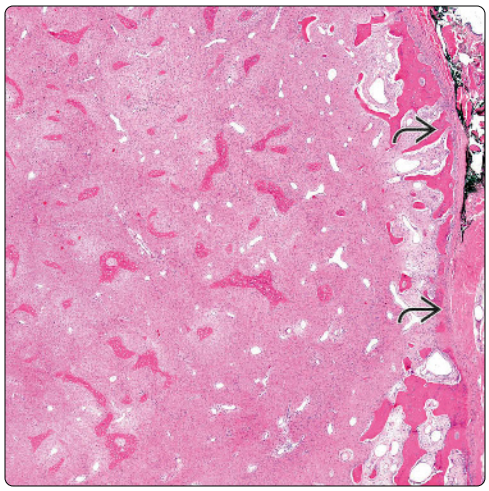


**(Left)** *Fibrous dysplasia with cartilage located in the medullary cavity of a bone is shown. The cartilaginous component appears as nodules and plate-like structures of pearly white-gray tissue* ⇨*. The bone-containing element is tan and has a trabeculated appearance* ➡*.* **(Right)** *Polyostotic fibrous dysplasia involving the small bones of the foot is shown. There are multiple gray-white lesions involving the medullary cavities* ⇨*.*

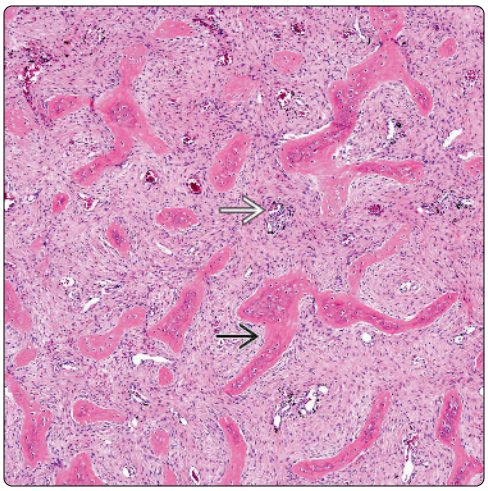


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**Fibrous Dysplasia With Sharp Margin**

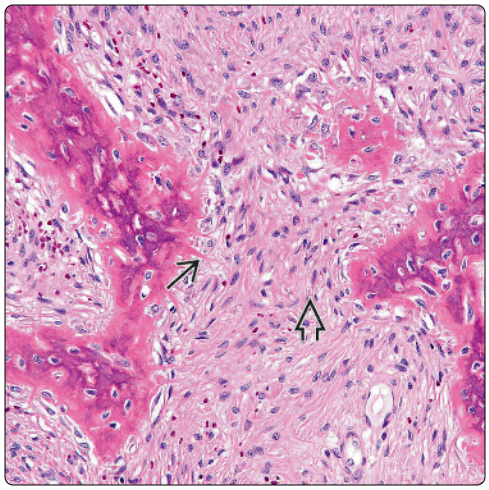


**Complex Pattern of Woven Bone**

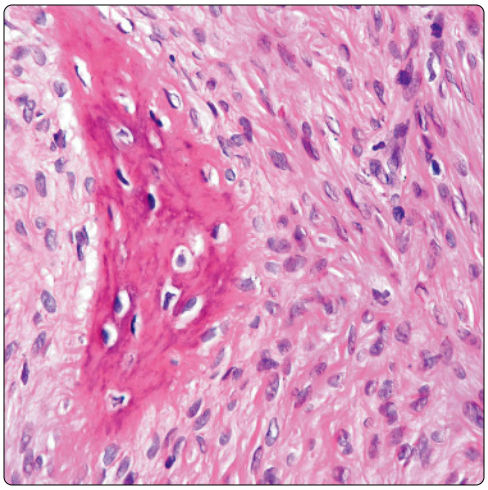


**(Left)** *Low-power view of fibrous dysplasia demonstrates its well-defined margin of growth. The solid, bone-containing mass is delineated by a rim of reactive subperiosteal new bone. (Right) Irregular curvilinear trabeculae of woven bone are characteristic of fibrous dysplasia. The bone is surrounded by a fibrous-appearing stroma that contains scattered congested blood vessels. The amount of bone in an individual tumor can be very variable.*

**Woven Bone and Spindle Cells**

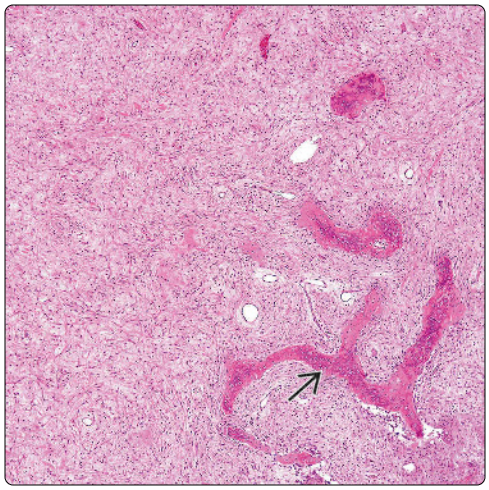


**Spindle Cells in Fibrous Dysplasia**

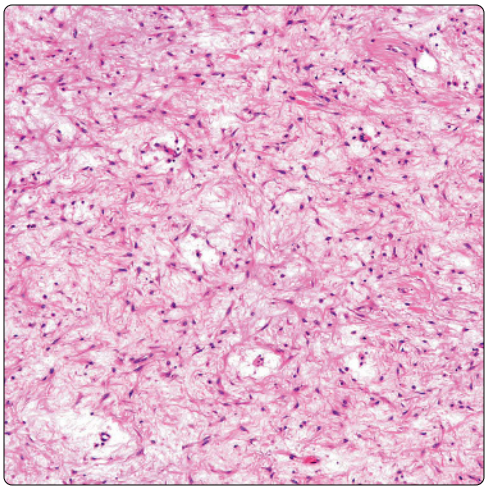


**(Left)** *High-power view of the neoplastic bone in fibrous dysplasia shows its composition of woven bone. Sharpey-like collagen fibers of the stroma can be seen extending into the matrix. The fibrous stroma is moderately cellular.* **(Right)** *Neoplastic trabecular bone of fibrous dysplasia is woven in architecture. The bone lacks prominent osteoblastic rimming and is surrounded by a fibroblastic-appearing stroma. The stroma cells are arranged in a whorling pattern.*

**Stromal-Rich Area in Fibrous Dysplasia**



**Fibromyxoid Appearance**

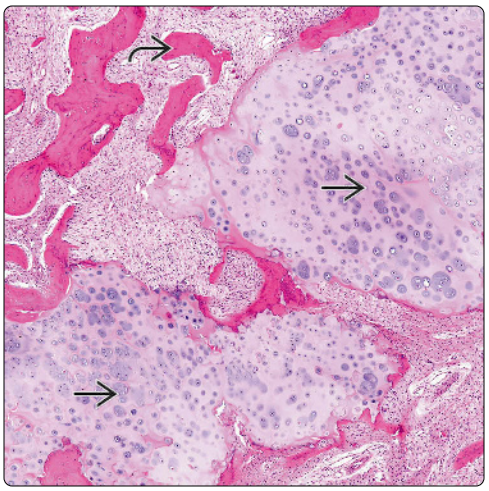


**(Left)** *Fibrous dysplasia can contain areas in which there is little or no neoplastic bone, as in this case. These regions may be fibroblastic or myxomatous in appearance and cause diagnostic difficulties, especially on limited biopsies.* **(Right)** *This case of fibrous dysplasia contains regions with no neoplastic bone. The tissue is fibromyxoid in appearance. The neoplastic spindle and stellate cells are cytologically bland and do not show mitotic activity.*

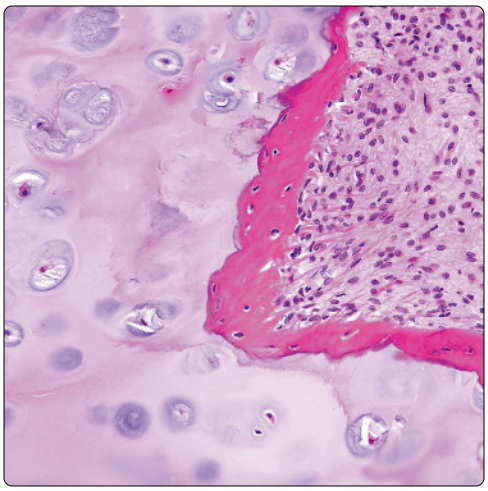


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### Fibrous Dysplasia With Cartilage Nodules



### Cartilage Nodules in Fibrous Dysplasia

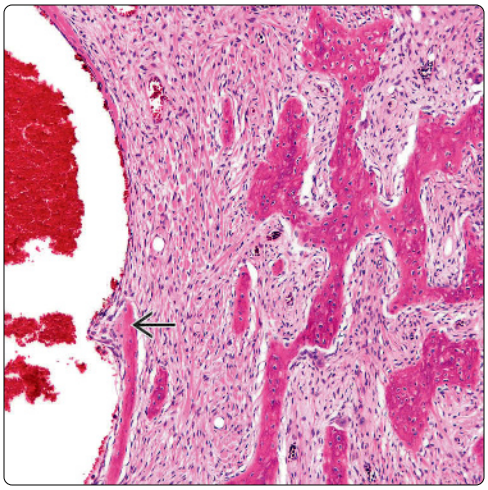


**(Left)** *Fibrous dysplasia contains nodules of well-formed hyaline cartilage surrounded by bone. Adjacent areas are composed of fibroosseous tissue that is characteristic of fibrous dysplasia.* **(Right)** *A cartilaginous component of fibrous dysplasia shows the well-formed hyaline cartilage. The bland chondrocytes have an architectural arrangement that can mimic a growth plate. Note the woven bone trabeculum and adjacent fibrous stroma that is typical of fibrous dysplasia.*

### Cysts in Fibrous Dysplasia

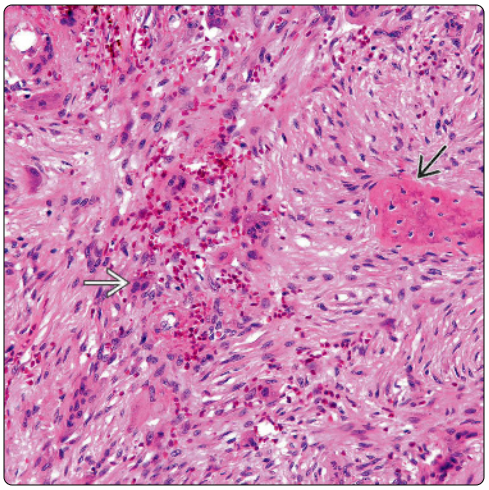


### Cyst Wall in Fibrous Dysplasia

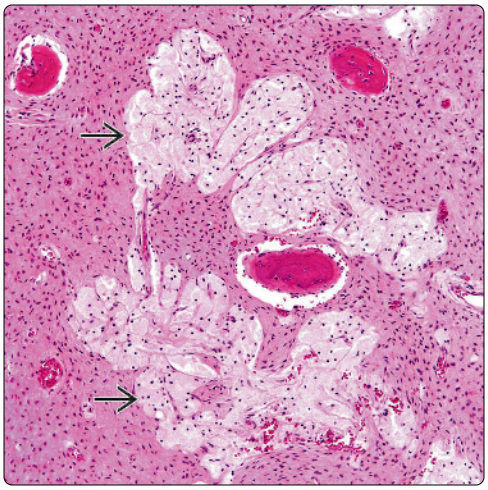


**(Left)** *Low-power view shows fibrous dysplasia of the rib containing a cystic component containing blood and fibrin aggregates. The tumor expands the rib and is well demarcated; it is surrounded by a rim of reactive bone. The majority of the tumor is solid in appearance.* **(Right)** *Wall of a cyst in fibrous dysplasia is composed mainly of the fibrous component with a small trabeculum of woven bone. Sometimes the cyst wall can resemble that of an aneurysmal bone cyst.*

### Hemorrhage and Giant Cells



### Foam Cells in Fibrous Dysplasia



**(Left)** *Fibrous dysplasia sometimes contains areas of hemorrhage associated with multinucleated osteoclast-type giant cells. This alteration can mimic giant cell reparative granuloma and solid aneurysmal bone cyst. Note the woven bone trabeculum that is typical of fibrous dysplasia.* **(Right)** *Other changes that can occur in fibrous dysplasia are the presence of collections of foamy macrophages. These foci can resemble fibroxanthoma or nonossifying fibroma.*



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KEY FACTS

## TERMINOLOGY

- Liposclerosing fibromyxoid tumor (LSMFT)

## CLINICAL ISSUES

- Almost always located in intertrochanteric region of proximal femur
  - Rarely originates in other long bones and pelvis
- Usually asymptomatic
  - May be detected during work-up for another disease process, such as staging for carcinoma
- Behaves in benign fashion with very small percentage undergoing malignant transformation

## IMAGING

- Well-defined margins
- Tumor is mixed radiodense and lucent and can have ground-glass appearance

## MACROSCOPIC

- Well-defined tumor
- Firm, tan-white-yellow in appearance

## MICROSCOPIC

- Lesion is composed of constellation of histological features
  - Intralesional bone woven bone with prominent cement lines
  - Fibrous and myxofibrous areas
  - Fibroxanthomatous areas
  - Adipose tissue with fat necrosis

## TOP DIFFERENTIAL DIAGNOSES

- Fibrous dysplasia
- Intraosseous lipoma
- Bone infarction

## DIAGNOSTIC CHECKLIST

- Think of LSFMT for benign tumors containing bone, fibrous tissue, and fat in proximal femur

**Radiograph**



**Large Liposclerosing Myxofibrous Tumor**

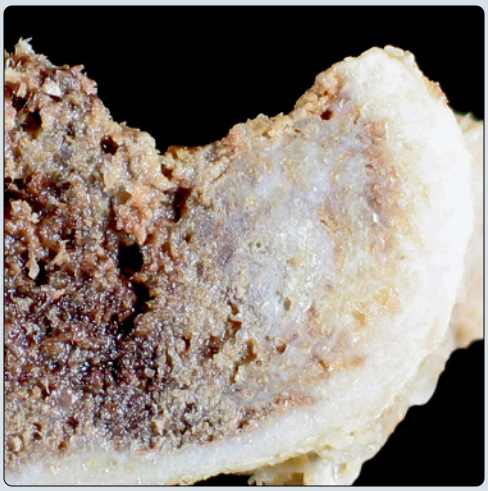


**(Left)** *AP radiograph shows a fairly dense, sclerotic, round lesion located in the intertrochanteric region, typical of liposclerosing fibromyxoid tumor (LSMFT). Note the presence of a sclerotic rim.* **(Right)** *LSMFT expanding the greater trochanter and extending into the base of the femoral neck is shown. The margin is well defined and irregular. The tumor is mixed radiolucent and radiodense and has a bubbly appearance.*

**Trabeculated Pattern**



**Gray-Tan Tumor**



**(Left)** *Plain radiograph of the proximal portion of the femur shows a liposclerosing myxofibrous tumor with a well-defined sclerotic margin in the intertrochanteric region. Intralesional mineralized matrix is present and in areas has a trabeculated pattern.* **(Right)** *Excised LSMFT appears as a gray-tan-yellow mass within the medullary cavity of the femur. The adjacent cortex is unremarkable, and there is no periosteal reaction.*



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## TERMINOLOGY

### Abbreviations

- Liposclerosing myxofibrous tumor (LSMFT)

### Synonyms

- Polymorphic fibroosseous lesion
- Polymorphic fibrous dysplasia
- Polymorphic fibrocystic disease of bone
- Atypical fibrous dysplasia

### Definitions

- Benign fibroosseous lesion that may represent variant of fibrous dysplasia

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Rare lesion
  - Not recognized as unique entity by major textbooks on orthopedic pathology
- Age
  - Affects adults
    - Mean age in one series: 42 years
- Sex
  - Slight male predominance

### Site

- Usually located in intertrochanteric region of proximal femur
  - Involvement of pelvis and long tubular bone is rare

### Presentation

- Usually asymptomatic
- Incidental x-ray finding
- Occasionally pain
- Rarely pathologic fracture

### Natural History

- Lesions behave in benign fashion
  - Rarely reported to undergo malignant transformation
    - One series found that risk of malignant transformation was 10% (probably overestimation)

### Treatment

- Surgical approaches
  - Symptomatic lesions: Curettage and packing

## IMAGING

### Radiographic Findings

- Well-defined lytic lesion
- Marginal sclerosis is invariably present
- Mineralized matrix within lesion
  - Patterns of mineralization include globular, linear, small rounded, and arch-like configurations
- May have ground-glass appearance
- Bone contour either normal or mildly expansile

### MR Findings

- T1WI: Relatively homogeneous with signal intensity similar to skeletal muscle
- T2WI: Heterogeneous with high signal intensity (corresponding to fat) and decreased signal intensity (corresponding to mineralization)

### CT Findings

- Useful in characterizing marginal sclerosis and mineralization of matrix
- Demonstrates FDG uptake on PET CT

### Bone Scan

- Variably increased activity varying from mild to marked

## MICROSCOPIC

### Histologic Features

- Lesion is composed of constellation of histological features
  - Intralesional lamellar and woven bone
    - Curvilinear and circular bone similar to fibrous dysplasia
  - Pseudopagetoid bone
  - Irregulare woven bone (ischemic bone) with mineralization
  - Fibrous and myxofibrous areas
  - Fibroxanthomatous areas
  - Adipose tissue with fat necrosis
  - Cystic changes

## ANCILLARY TESTS

### Genetic Testing

- Point mutations in *GNAS* have been identified in LSMFT

## DIFFERENTIAL DIAGNOSIS

### Fibrous Dysplasia

- Woven bone trabeculae are randomly arranged in irregular and curvilinear patterns
- Fibrous dysplasia is less heterogeneous than LSMFT
- Evidence suggests that LSFMT (or subset) is histological variant of fibrous dysplasia
  - Proximal femur is commonly affected in fibrous dysplasia
  - *GNAS* mutations commonly present fibrous dysplasia

### Intraosseous Lipoma

- Mature fat with fat necrosis, histiocytes, and fibrosis
- Delicate trabeculae of woven and lamellar bone are seen
- Lacks constellation of features seen in LSMFT

### Bone Infarct

- Infarcts are typically located in femoral head, not in inter- or subtrochanteric region of femur

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Think of LSFMT for benign tumors bone, fibrous tissue, and fat in proximal femur

## SELECTED REFERENCES

1. Kim J et al: FDG uptake in liposclerosing myxofibrous tumor causes upstaging of Hodgkin lymphoma. Clin Nucl Med. 40(4):325-7, 2015
2. Corsi A et al: Monostotic fibrous dysplasia of the proximal femur and liposclerosing myxofibrous tumor: which one is which? J Bone Miner Res. 21(12):1955-8, 2006



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**Well-Circumscribed Tumor**



**Fracture Through Tumor**



**(Left)** *The tumor is located in between the greater and lesser trochanters. The lesion has an irregular sclerotic margin and radiolucent and radiodense components, the latter being centrally located. The remainder of the femur is unremarkable.* **(Right)** *LSMFT has undergone sudden pathological fracture. The elongated tumor is well circumscribed and has a sclerotic margin. The tumor is mottled in appearance and has areas that are radiodense and radiolucent.*

**Sclerotic Tumor in Femoral Neck**



**Heterogeneous Mass**



**(Left)** *The neoplasm is located between the greater and lesser trochanters and extends into the inferior aspect of the femoral head. The mass is triangular, well demarcated, and has a ground-glass-like pattern of radiodensity with small oval radiolucencies.* **(Right)** *Coronal T1-weighted MR shows a large LSMFT that extends into the base of the femoral neck. The tumor is heterogeneous with dark areas corresponding to components of mineralized bone. The hyperintense foci likely contain lipid.*

**Heterogenous Tumor**



**Tan-White Tumor**

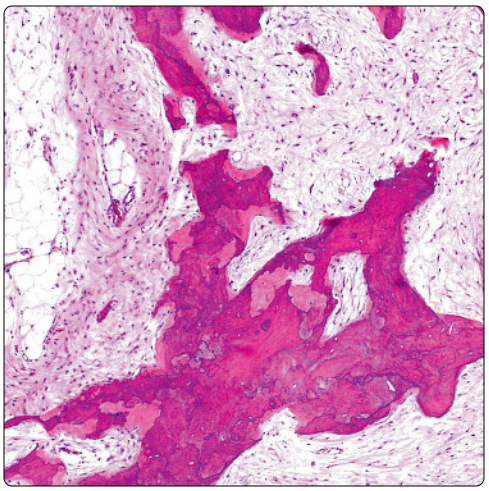


**(Left)** *Coronal T1-weighted MR of LSMFT involving the greater trochanter and base of the femoral neck is shown. The tumor is well circumscribed and has heterogeneous features.* **(Right)** *Resected femoral head contains an LSMFT in the base of the neck. The tumor is solid, has an irregular but well-circumscribed border, and varies from gray-white to pale yellow in appearance.*

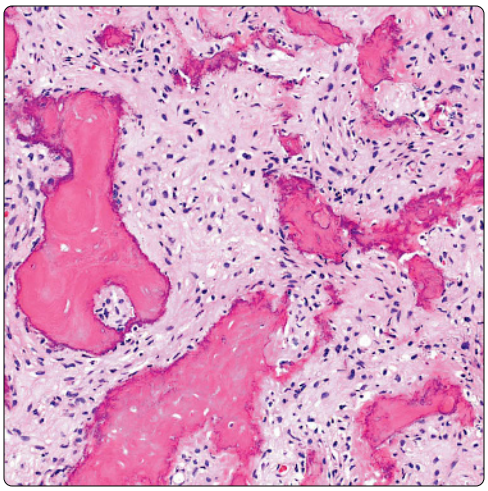


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### Fat, Fibrous Tissue, and Woven Bone

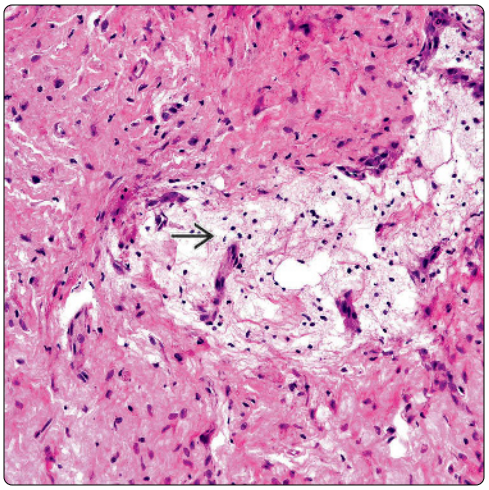


### Irregular Woven Bone Trabeculae

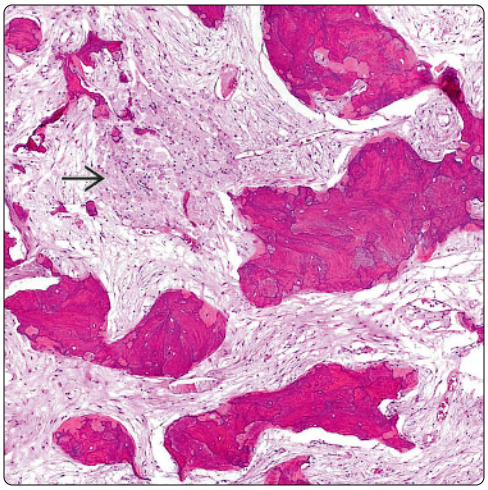


**(Left)** *Adipose tissue, fibrous tissue, and irregular, coarse woven bone are components of LSMFT. The lesion is relatively hypocellular and the proliferating spindle cells do not demonstrate any cytologic atypia.* **(Right)** *The woven bone trabeculae in this case of an LSMFT varies in size and is irregular in configuration. The intervening fibrous tissue is moderately cellular and the tumor cells have plump, dark, spindled nuclei. These features are reminiscent of fibrous dysplasia.*

### Fibrous Tissue and Foam Cells

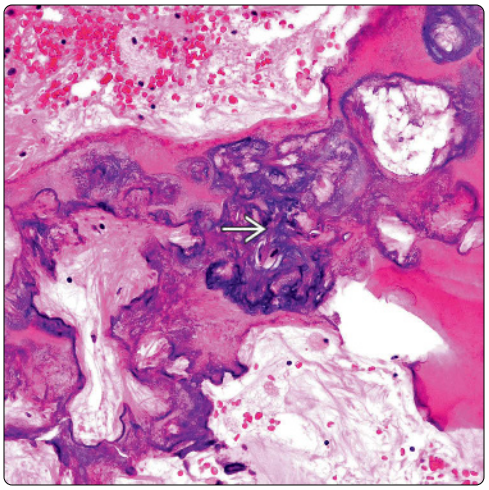


### Fibrous Tissue and Woven Bone

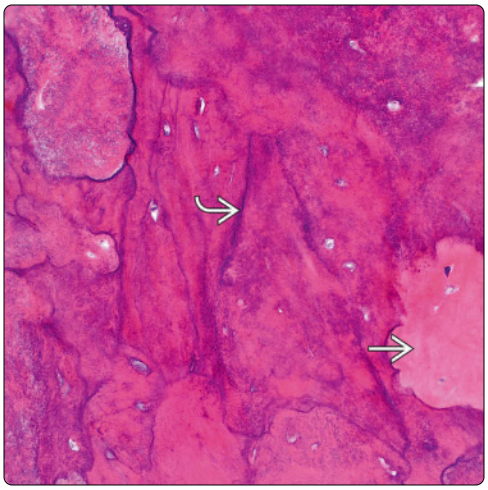


**(Left)** *This LSMFT contains stellate and spindle cells and a focus of foamy histiocytes. The lesional cells are cytologically bland and there is no mitotic activity. The foamy macrophages are usually arranged in clusters.* **(Right)** *The coarse, thick trabeculae of woven bone in the tumor can be curvilinear in configuration. Hypocellular fibrous tissue surrounds the bone and an island of foamy macrophages.*

### Calcified Bone



### Pseudopagetoid Woven Bone



**(Left)** *The matrix in this LSMFT consists of woven bone that is mineralized in an irregular fashion. The fibrous tissue surrounding the woven bone is hypocellular and hemorrhagic.* **(Right)** *The woven bone contains many cement lines and varies from pink (unmineralized) to red-purple (mineralized). The complexity of the cement lines mimics Paget disease of bone.*



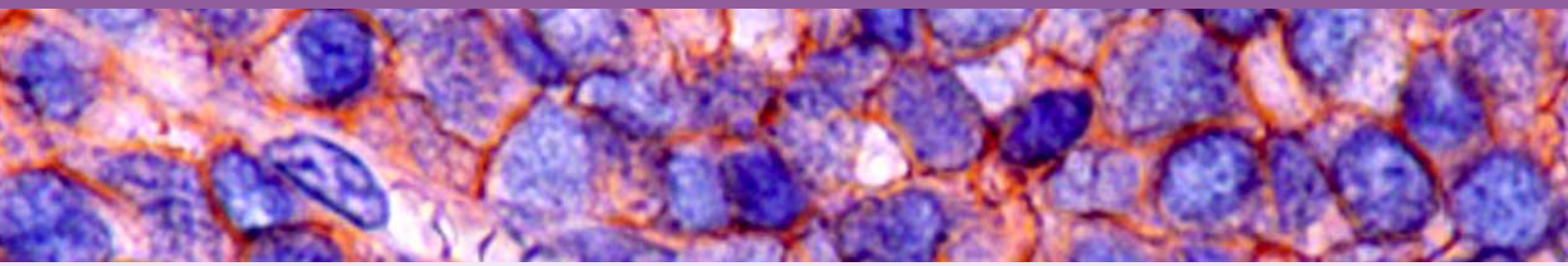
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SECTION 7

# Malignant Small Round Cell Tumors




Ewing Sarcoma and Related Tumors **218**
Melanotic Neuroectodermal Tumor **230**


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KEY FACTS

## TERMINOLOGY

- Malignant small round cell sarcoma
- Tumors composed of malignant small round &/or spindle cells that lack characteristic translocation designated Ewing sarcoma (EWS)-like family of tumors

## CLINICAL ISSUES

- Accounts for 6-10% of primary malignant bone tumors
- Diaphysis of long bones and flat bones of pelvis
- Treated with chemotherapy and surgery
- Chemotherapy improved prognosis to 75% 5-year survival
- Tumor should be extensively sampled histologically to assess chemotherapy induced necrosis

## IMAGING

- Destructive and lytic

## MACROSCOPIC

- Tan-white; usually transgresses cortex producing soft tissue mass

## MICROSCOPIC

- Tumor cells are 1-2x size of lymphocytes
- Sheets or irregular islands of cells
- Neural features: Organoid and Homer Wright rosettes
- Cells express CD99 (90%) and FLI-1 (90%)
- Fusion negative tumors may have spindle cells

## ANCILLARY TESTS

- *EWSR1*-negative tumors have uncommon fusions
- 85% of harbor t(11;22)(q24;q12) translocation

## TOP DIFFERENTIAL DIAGNOSES

- Malignant lymphoma
- Small cell osteosarcoma
- Mesenchymal chondrosarcoma
- Neuroblastoma

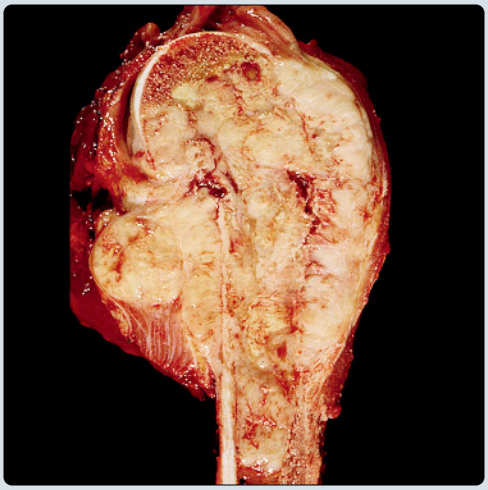
## DIAGNOSTIC CHECKLIST

- Sheets of malignant small round cells: Think EWS/PNET

**Destructive Poorly Defined Tumor**

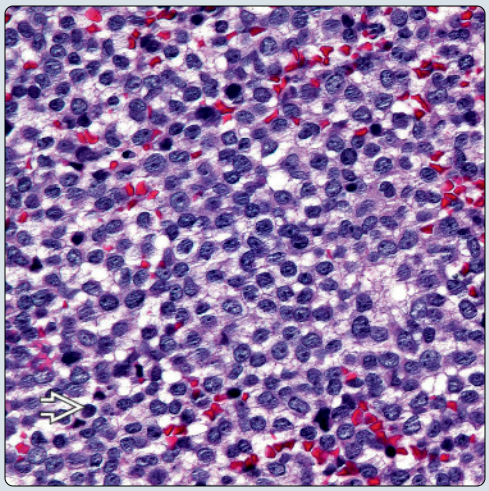


**Tumor Extending Into Soft Tissue**

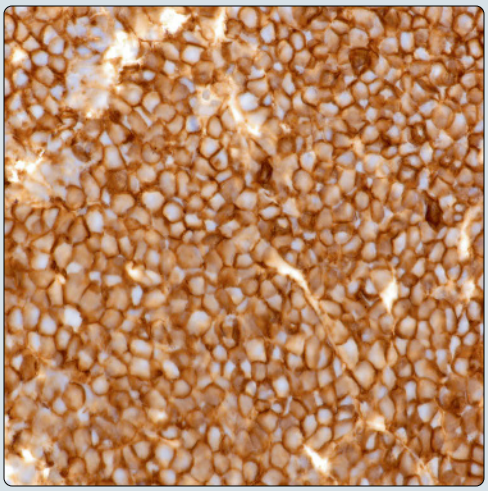


**(Left)** *Radiograph of a Ewing sarcoma shows a highly aggressive and ill-defined destructive mass in the proximal humerus. The mass has broken through the cortex and extended into the adjacent soft tissues.* **(Right)** *Ewing sarcoma arising in the metadiaphysis of the humerus manifests as a fleshy mass centered in the medullary cavity, breaking through the cortex and forming a circumferential soft tissue mass.*

**Sheets of Round Cells**



**Membranous Staining for CD99**



**(Left)** *High-power view of Ewing sarcoma shows that the neoplastic cells have a sheet-like growth pattern, finely dispersed chromatin, and clear (glycogen-rich) cytoplasm with well-defined cell membranes. There are scattered apoptotic cells throughout the tumor* ⇨. **(Right)** *Ewing sarcoma expresses a variety of antigens. CD99 is strongly expressed in most cases and often has a membranous pattern. The staining for CD99 is characteristic but not diagnostic of Ewing sarcoma as many other types of tumors are positive.*



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## TERMINOLOGY

### Abbreviations

- Ewing sarcoma (EWS)

### Synonyms

- Peripheral neuroepithelioma
- Askin tumor
- Primitive neuroectodermal tumor (PNET)

### Definitions

- Round cell sarcoma showing variable degree of neuroectodermal differentiation
  - Undifferentiated tumors have been diagnosed as EWS
  - Tumors demonstrating neuroectodermal differentiation by light microscopy, immunohistochemistry, or electron microscopy previously designated PNET (term removed from WHO)
  - Tumors composed of malignant small round &/or spindle cells that lack characteristic translocation designated EWS-like family of tumors

## ETIOLOGY/PATHOGENESIS

### Neoplasm

- Evidence suggests stem cell origin

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Accounts for 6-10% of primary malignant bone tumors
    - Follows osteosarcoma and chondrosarcoma in frequency in adults and osteosarcoma in children and adolescents
- Age
  - Most patients between 10-15 years
  - ~ 80% are younger than 20 years
- Sex
  - Boys affected more frequently than girls (1.3-1.4:1)
  - *BCOR*-rearranged tumors have striking male predominance
- Ethnicity
  - Predilection for whites (3/1,000,000); Africans, Asians, and Native Americans rarely affected (0.2/1,000,000)

### Site

- Arise in any portion of skeleton
  - Usually develops in diaphysis or metadiaphysis of long bones and pelvis
- ~ 22% of cases arise in femur followed by ilium, tibia, humerus, fibula, and ribs

### Presentation

- Painful enlarging mass
- Some patients have systemic findings that mimic infection: Fever, elevated sedimentation rate, anemia, and leukocytosis
- Pathologic fracture is uncommon

### Treatment

- Usually treated with combination of chemotherapy and surgery
- Chemotherapy is usually given preoperatively, which allows for pathologic assessment of subsequent surgical specimen for effectiveness of drug regimen
- Chemotherapy-induced necrosis ≥ 90% is considered good response
- Therapy-related cytologic changes of tumor cells are uncommon
  - Changes include ganglion cell differentiation, marked enlargement, hyperchromasia, pleomorphism, and presence of rhabdoid-like cells
- Radiotherapy is reserved for tumors located in surgically inaccessible sites, surgical beds with inadequate margins, and palliation
- Tumor should be extensively sampled histologically to assess chemotherapy-induced necrosis

### Prognosis

- Effective chemotherapy has improved prognosis to 75% 5-year survival
  - At least 50% are long-term cures
- Prognostic factors include stage of disease at time of diagnosis and site of tumor
- Other important factors
  - Amount of chemotherapy-induced tumor necrosis, development of local recurrence or metastasis
- *BCOR* and *CIC-DUX4*-rearranged tumors are aggressive, do not respond well to EWS chemotherapy, and have poor prognosis

## IMAGING

### Radiographic Findings

- Destructive and lytic with poorly defined margins
  - Often underestimates extent of tumor; clarified by MR
- Permeation of cortex usually results in concentric soft tissue mass that can be very large
- Extraosseous tumor frequently erodes outer cortex producing "saucerization" of bone
- Displaced periosteum deposits layers of reactive bone in onion skin-like or sunburst-like fashion
- Tumor diminishes in size, sometimes completely, after therapy

### MR Findings

- Identifies extent of tumor in bone and soft tissue
- Low signal intensity on T1- and high signal on T2-weighted images
- Useful in assessing postchemotherapy tumor viability

### CT Findings

- Large, destructive mass

### Bone Scan

- Tumor has avid uptake of radionuclides

## MACROSCOPIC

### General Features

- Tan-white, fish flesh-like; transgresses cortex producing soft tissue mass
- Frequently contains areas of hemorrhage and necrosis
- Thin layers of reactive bone underpin raised periosteum
- Intramedullary margins of tumor poorly defined



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## MICROSCOPIC

### Histologic Features

- Tumor cells are 1-2x size of lymphocytes with scant cytoplasm
- Tumor cells grow in sheets or irregular islands delineated by dense fibrous tissue
- Architectural features suggestive of neural differentiation include organoid growth pattern and Homer Wright rosettes
- Oval nuclei with finely distributed chromatin and inconspicuous nucleoli; scant eosinophilic or clear cytoplasm
- Occasionally, tumor cells are larger and have irregular nuclear contours and prominent nucleoli
- Islands of tumor cells may show palisading and cording, known as adamantinoma-like variant
- Mitoses may be infrequent or numerous and necrosis can be extensive
- Stroma is scant, lymphoid infiltrate absent, and supportive vascular tree is inconspicuous
- *BCOR-CCNB3* tumors composed of heterogeneous small round and spindle cells, and stroma may be myxoid
  - Short spindle cells may predominate
- *CIC-DUX4* tumors composed of sheets of small round cells; less monotonous than EWS, mild nuclear pleomorphism, vesicular chromatin, may have conspicuous nucleoli, and more cytoplasm
  - Spindle cells and myxoid stroma may be present

### Ultrastructural Features

- Primitive cells with few organelles; glycogen may be abundant
- Neural differentiation suggested by interdigitating cytoplasmic cell processes connected by primitive junctions, scattered microtubules, and neurosecretory granules
- Definite tonofibrils and well-developed basal lamina can be identified in some keratin-positive tumors

## ANCILLARY TESTS

### Immunohistochemistry

- Cells express vimentin, CD99 (90%), and FLI-1 (90%)
  - CD99 is also expressed by many other malignant small round cell tumors, including lymphoblastic lymphoma, small cell osteosarcoma, mesenchymal chondrosarcoma, and small cell carcinoma
    - Small cell osteosarcoma and mesenchymal chondrosarcoma are negative for FLI-1
  - Negative staining for CD99 stain should raise possibility that tumor may not be EWS/PNET
  - Tumors with neuroectodermal differentiation express 1 or more neural markers, including NSE, CD57, or S100
- Neurofilament and keratin positivity is seen in ~ 20% of cases
- *BCOR-CCNB3* and *CIC-DUX4* tumors usually patchy CD99 positive, can be diffuse
- *CIC-DUX4* tumors stain for WT1, ETV6, and CIC
- *BCOR-CCNB3* tumors stain for BCOR and CCNB3

### Molecular Pathology

- Most EWS have translocation between *EWSR1* and member of ETS gene family; 85% harbor t(11;22)(q24;q12)
- 5-10% have t(21;22)(q22;q12)
- < 1% of tumors show *EWSR1* (EWS) fusion with *ETV1* (7p22), *ETV4* (E1AF) (17q12), or *FEV* (2q33)
- Fusion genes generated from translocations important in genesis of tumor
  - Chimeric proteins function as aberrant transcription factors determining biological behavior
- *EWSR1*-negative tumors have uncommon fusions
  - *CIC-DUX4* fusion; accounts for 2/3 of *EWSR1*-negative tumors; most occur in soft tissue
  - *BCOR-CCNB3*; *BCOR-MAML3*; *ZC3H7B-BCOR* fusion; most occur in bone
  - *FUS-ERG* and *CIC-FOXO4* fusions rare

## DIFFERENTIAL DIAGNOSIS

### Malignant Lymphoma

- Cells in large cell lymphoma often larger, have irregular nuclei and more cytoplasm, express lymphoid antigens, have different genetic aberrations
- Lymphoblastic lymphoma composed of uniform round cells and frequently contains admixed benign infiltrating lymphocytes
  - CD99 positive but FLI-1 negative and TdT positive

### Neuroblastoma

- Metastatic undifferentiated neuroblastoma can be difficult to distinguish from EWS/PNET on histology
  - Negative for CD99 and FLI-1; N-MYC amplified
- Neuropil and ganglion cell differentiation helpful features
- Neuroblastoma has loss of chromosome 1p and does not have translocation involving chromosome 22

### Small Cell Osteosarcoma

- Presence of matrix excludes EWS
  - Reactive woven bone in EWS can cause confusion with osteosarcoma; look for osteoblastic rimming

### Mesenchymal Chondrosarcoma

- Areas of chondroid differentiation admixed with malignant small round cell component
- Tumor has nodular architecture and prominent vascular tree that frequently has hemangiopericytoma-like pattern, which is usually not present in EWS/PNET

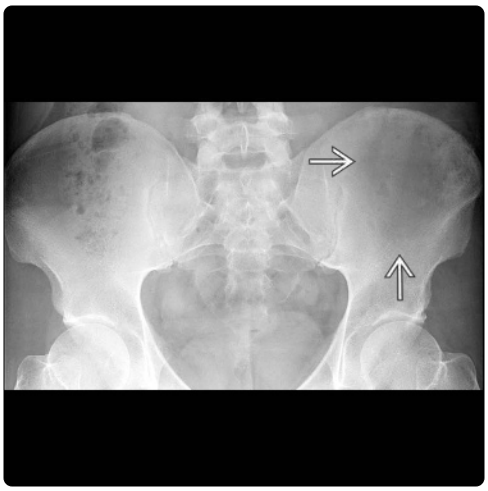
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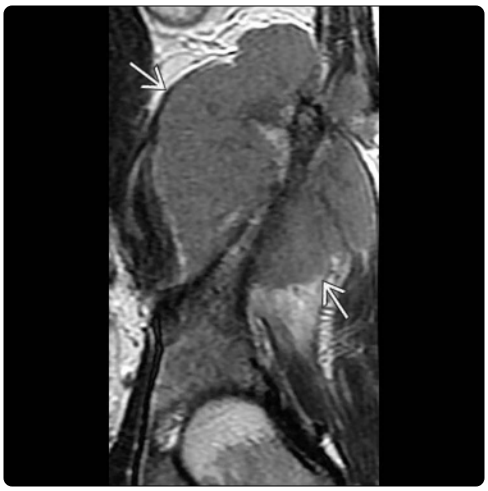



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**Subtle Lytic Mass in Ilium**



**Large Soft Tissue Component**



**(Left)** *Ewing sarcoma of the pelvis often produces subtle lytic destruction of the bone and is large at the time of diagnosis. In this case, the body of the left ilium has a large area of poorly defined lysis ➔. (Right) Accompanying sagittal MR of the pelvis radiograph shows that the Ewing sarcoma replaces the medullary cavity and forms a large intra- and extrapelvic mass ➔.*

**Large Eccentric Soft Tissue Mass**



**Large Mass Involving Bone and Soft Tissue**

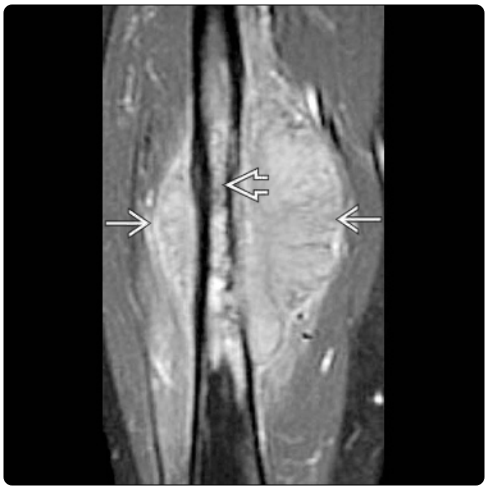


**(Left)** *The tumor involves the distal femoral medullary cavity and grows eccentrically into the soft tissues posteriorly ➔. The posterior cortex shows irregular resorption with a periosteal reaction.* **(Right)** *The sagittal T2-weighted MR shows that the Ewing sarcoma replaces much of the medullary cavity of the distal femoral diaphysis and metaphysis and forms a large posterior and small anterior soft tissue components ➔.*

**Erosion of Cortex With Soft Tissue Mass**



**Large Mass**

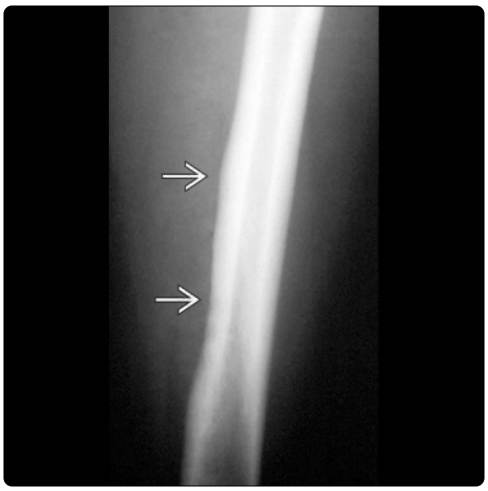


**(Left)** *Radiograph of Ewing sarcoma shows a large saucerization defect along the femoral shaft ➔ causing thinning of the cortex. This results from the tumor permeating the cortex, forming an extraosseous soft tissue mass. A Codman triangle is seen proximally ➔.* **(Right)** *T1-weighted, contrast-enhanced coronal MR with fat saturation shows a large Ewing sarcoma arising in the diaphysis of the femur and extending into adjacent soft tissues ➔, causing saucerization of the medial femoral shaft ➔.*

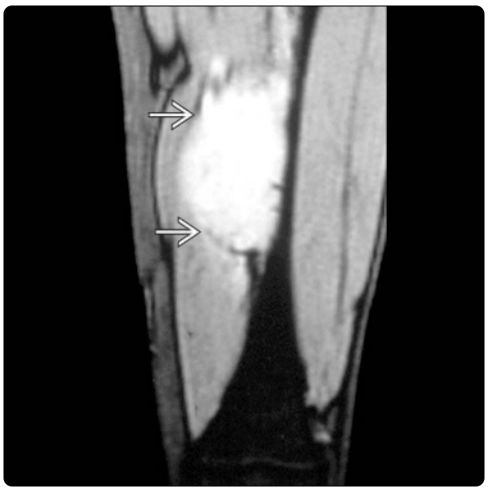


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### Saucerization of Cortex



### Eccentric Large Tumor

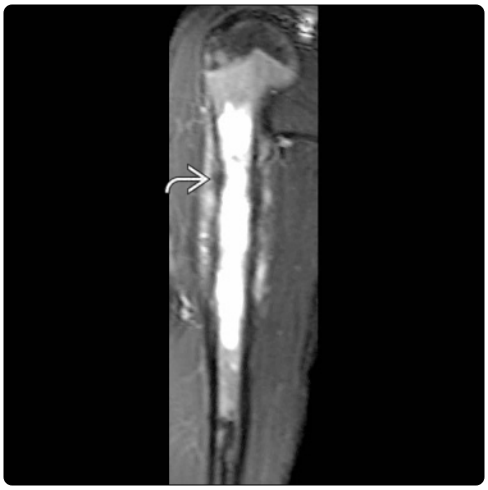


**(Left)** *Radiograph shows Ewing sarcoma arising in the diaphysis of the femur, producing a slight increase in density within the medullary cavity. The tumor has extended into adjacent soft tissues, causing secondary subtle saucerization defect.* **(Right)** *MR shows Ewing sarcoma arising in the shaft of the mid diaphysis of the femur, forming a large, hyperintense mass in the adjacent lateral soft tissues. The intramedullary component is barely visible in this image.*

### Poorly Defined Lysis



### Elongate Medullary Tumor

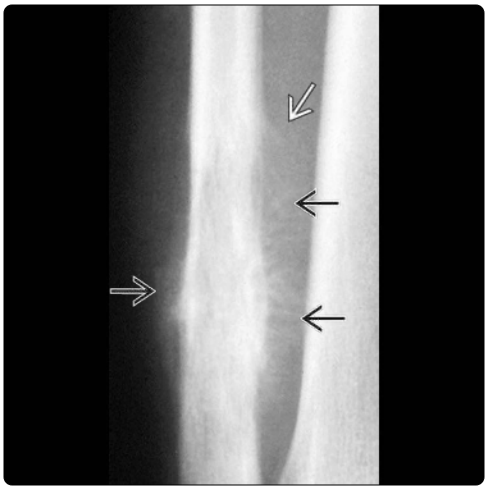


**(Left)** *Radiograph of a Ewing sarcoma in the proximal humerus shows a lucent lesion with areas of endosteal resorption and periosteal new bone formation along the medial and lateral cortices. The margins are poorly defined.* **(Right)** *Coronal T2-weighted MR of a Ewing sarcoma shows hyperintense signal replacing a long segment of the marrow in the humeral shaft with permeation of tumor through a thinned cortex. The linear dark signal perpendicular to the cortex represents sunburst periosteal new bone.*

### Onion Skin Periosteal Reaction



### Sunburst Pattern

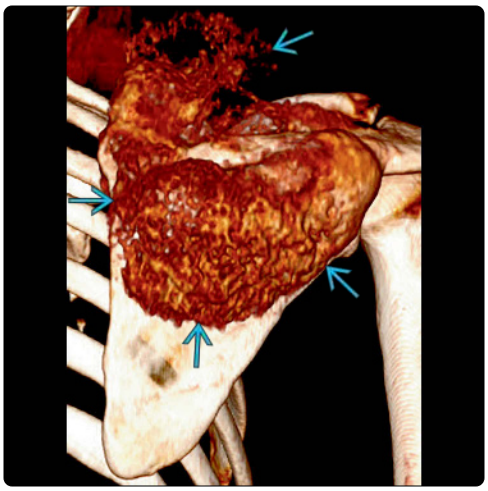


**(Left)** *Radiograph of Ewing sarcoma shows the typical onion peel multilayered appearance of periosteal new bone formation along the cortices. The tumor is poorly defined and invades into the soft tissues, forming a subtle mass.* **(Right)** *Radiograph of a Ewing sarcoma of the fibula shows the typical thin, linear, and sunburst periosteal reaction around a highly permeative, aggressive tumor. A Codman triangle is present along the medial proximal cortex.*



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Large Scapular Mass



Large Tumor of Scapula

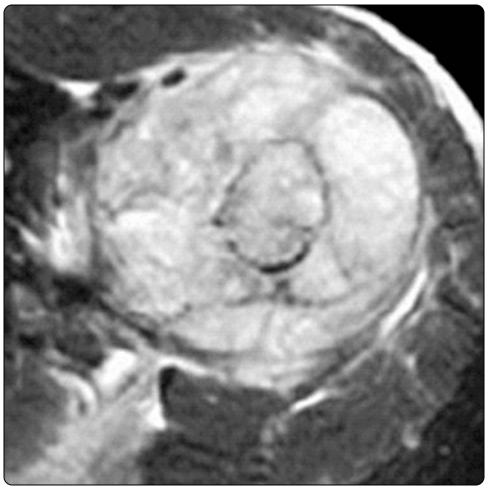


**(Left)** *Ewing sarcoma of the body of the scapula extends into the posterior soft tissues forming a large mass. In this 3D reformatted CT, the tumor appears as an irregular-surfaced red-brown mass.* **(Right)** *Axial T2-weighted fat saturated MR shows an extremely large mass centered in the scapula forms very prominent anterior and posterior soft tissue components and involves the glenoid.*

Large destructive Tumor

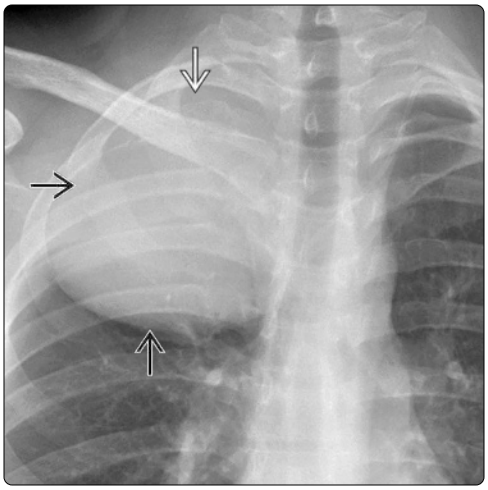


Circumferential Soft Tissue Mass

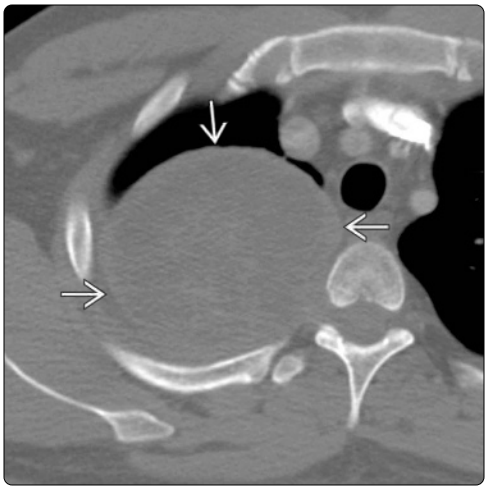


**(Left)** *T1-weighted coronal MR of a Ewing sarcoma arising in the proximal humerus shows a marrow-replacing lesion that is highly aggressive, extends through the cortex, and forms a large soft tissue mass.* **(Right)** *T2-weighted axial MR shows a Ewing sarcoma within the humerus presenting as a large, hyperintense, lobulated mass. The tumor replaces the marrow cavity, penetrates and destroys the cortex, and forms a large circumferential soft tissue mass.*

Thoracic Tumor



Chest Wall Tumor



**(Left)** *Radiograph shows a Ewing sarcoma (Askin tumor) involving the pleura and lung apex and destroying the posterior aspect of the 3rd rib. The oval mass shows uniform increased radiodensity.* **(Right)** *Axial CT shows a large Ewing sarcoma arising from the posterior chest wall (Askin tumor) with slightly heterogeneous density. The tumor arises in an adjacent rib that is not visible in this image and extends into the thoracic cavity, where it compresses the adjacent lung.*



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**Lytic Mass in Calcaneus**

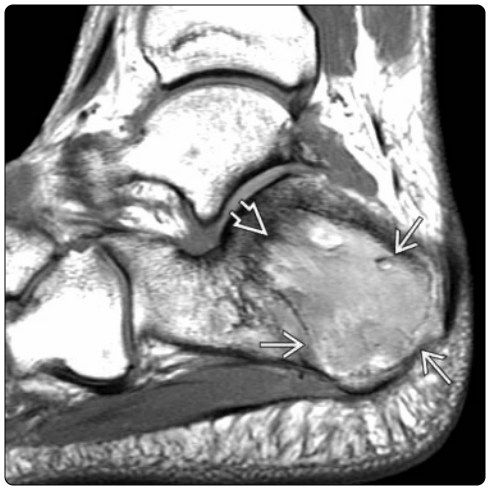


**Lytic Mass of Calcaneus**



**(Left)** *Radiograph of a Ewing sarcoma arising in the calcaneus shows a vague lucent lesion in the posterior calcaneus surrounded by a thin, sclerotic rim. (Right) Sagittal reformatted CT of a calcaneal Ewing sarcoma shows a lytic lesion in the posterior calcaneus with fairly thick sclerotic margins superiorly and anteriorly. Prominent septation is seen within the lesion. The small linear ossified densities in the lesion may represent residual rebuttressed bone.*

**Marrow Replacing Mass**



**Nonenhancing Tumor**



**(Left)** *Sagittal T1-weighted MR of a Ewing sarcoma of the calcaneus shows a heterogeneous lesion in the posterior calcaneus with an ill-defined anterior margin. The thick, dark signal along the subtalar margin represents the superior bony margin. (Right) Axial T1-weighted MR of a Ewing sarcoma arising in the calcaneus, following intravenous gadolinium, shows a nonenhancing lesion with rim enhancement. There is also enhancement of the lateral soft tissues.*

**Cortical Mass**



**Lytic Mass**



**(Left)** *This radiograph of a round cell sarcoma with a BCOR-CCNB3 fusion shows a soft tissue density tumor associated with a periosteal laminated reaction proximally and distally. The underlying cortex shows very subtle saucerization. (Right) Accompanying lateral radiograph of previous AP radiograph of a round cell sarcoma with BCOR-CCNB3 fusion is shown. The tumor has a produced a relatively well-defined radiolucency of the tibial diaphysis.*

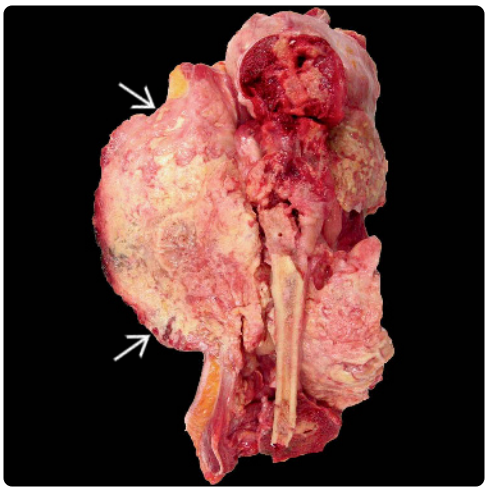


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### Fungating Mass

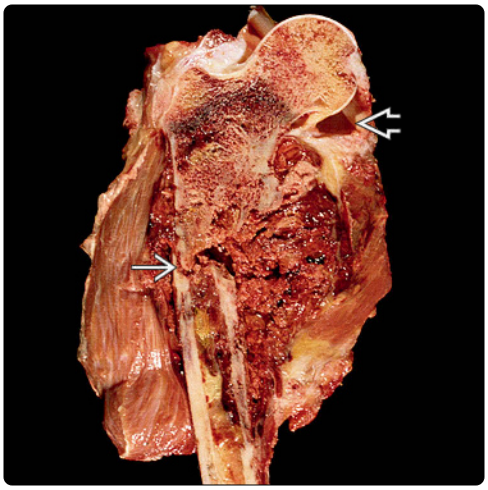


### Large Ulcerated Tumor

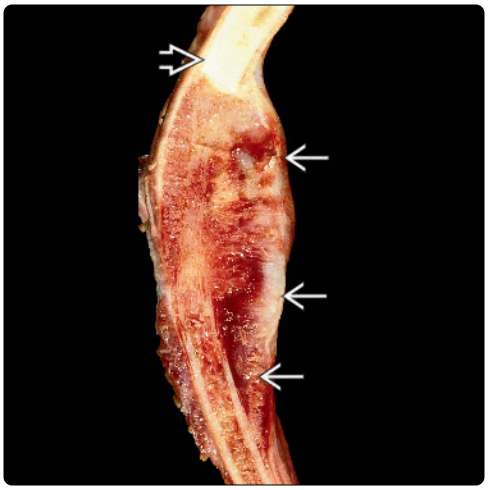


**(Left)** *This Ewing sarcoma has destroyed the underlying bone and has grown into the soft tissues forming a large ulcerated fungating mass.* **(Right)** *Sagittal section through a large Ewing sarcoma that arose in the tibia formed a circumferential soft tissue mass that has ulcerated the overlying skin ➡.*

### Mass With Pathologic Fracture



### Tumor Arising in Rib

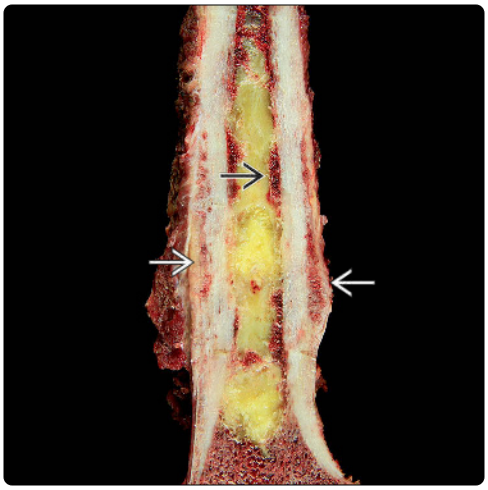


**(Left)** *This Ewing sarcoma of the proximal metadiaphysis of the femur manifests as a large, destructive hemorrhagic mass. The tumor erodes through the cortex, extends into the adjacent soft tissue, and has resulted in a pathologic fracture ➡; the adjacent hip joint is uninvolved ➡.* **(Right)** *This Ewing sarcoma of a rib (Askin tumor) arises in the medullary cavity close to the costal cartilage ➡ and extends into the adjacent soft tissue, lifting the periosteum ➡.*

### Hemorrhagic Tan Mass



### Treated Tumor

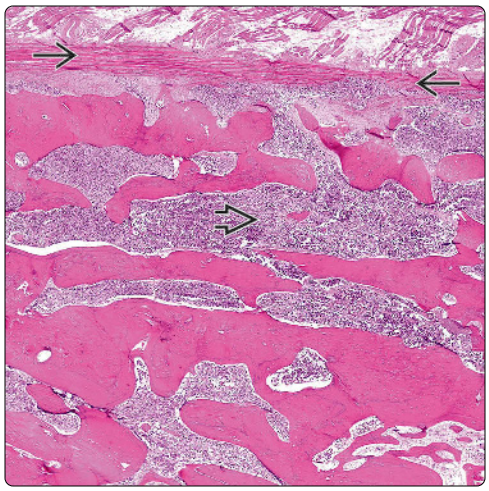


**(Left)** *A hemorrhagic round cell sarcoma with a BCOR-CCNB3 fusion arises in the medullary cavity of the distal humerus. The tumor transgresses the cortex and extends into the soft tissue.* **(Right)** *Ewing sarcoma of the humerus treated with preoperative chemotherapy shows extensive tumor necrosis. The tumor has undergone significant reduction in size and consists of soft tan, pale yellow necrotic tissue ➡ in the medullary cavity. Note that the periosteum is thickened by reactive bone ➡.*

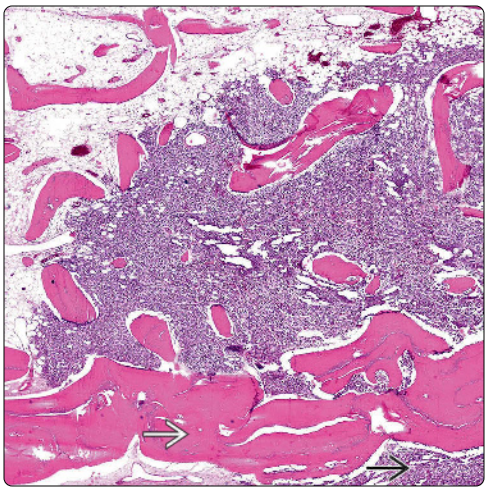


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**Permeation of Bone**

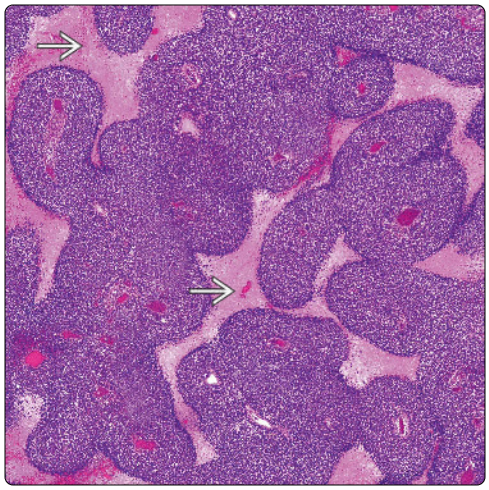


**Encasing Bony Trabecula**

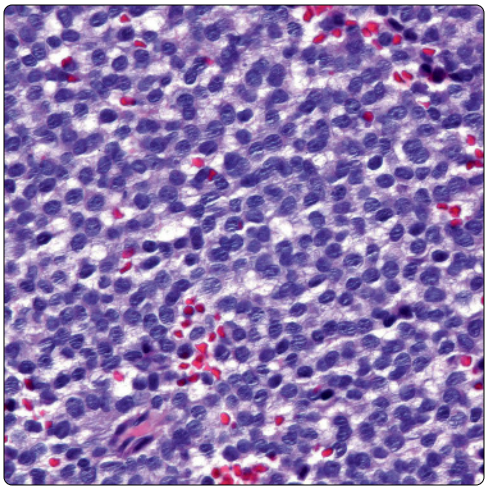


**(Left)** *Ewing sarcoma arising in the medullary cavity of bone demonstrates extensive infiltration of the cortex and extends to the surface periosteum, which separates the tumor from the surrounding soft tissues.* **(Right)** *Intramedullary portion of a Ewing sarcoma shows infiltrative growth pattern with neoplastic cells replacing the marrow space and encasing preexisting trabecular bone. Focally, the tumor permeates the cortex and extends into the periosteum.*

**Organoid Growth Pattern**

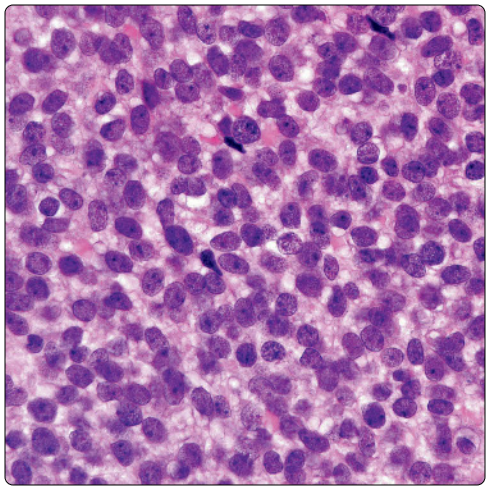


**Back-to-Back Cells**

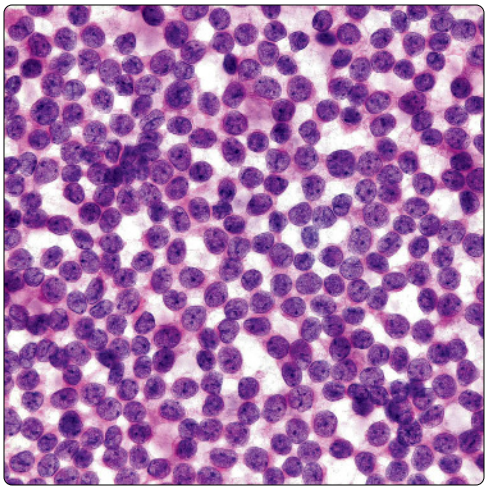


**(Left)** *An untreated Ewing sarcoma has a prominent organoid growth pattern with intervening fibrosis. This pattern is frequently seen in those tumors with neuroectodermal differentiation.* **(Right)** *Ewing sarcoma is typically composed of the sheets of small round cells with little cytoplasm. The cytoplasm can be eosinophilic or clear, and in this case, it is clear. The clearing represents intracytoplasmic glycogen.*

**Round Cells With Clear Cytoplasm**



**Fine Chromatin**

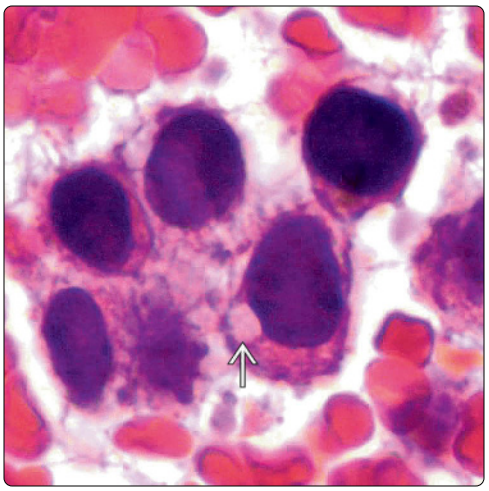


**(Left)** *Ewing sarcoma shows that the neoplastic cells grow in sheets, are homogeneous, and have finely dispersed chromatin, small nucleoli, and clear cytoplasm caused by intracytoplasmic glycogen.* **(Right)** *A touch prep of Ewing sarcoma demonstrates the uniformity of the neoplastic cells. The cells are small, round, regular in size and shape with no nuclear irregularity and exhibit a fine chromatin pattern; some have small nucleoli.*

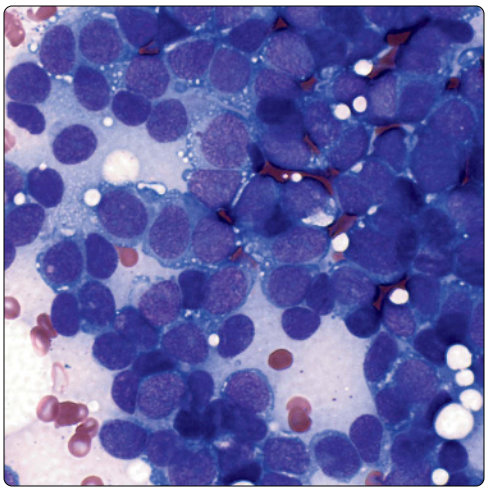


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### Oval Cells With Eosinophilic Cytoplasm

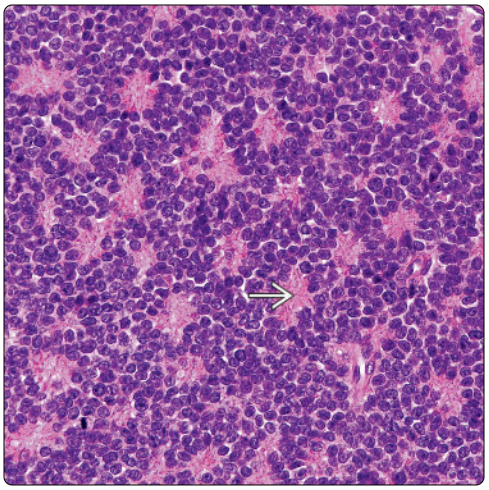


### Primitive Cells

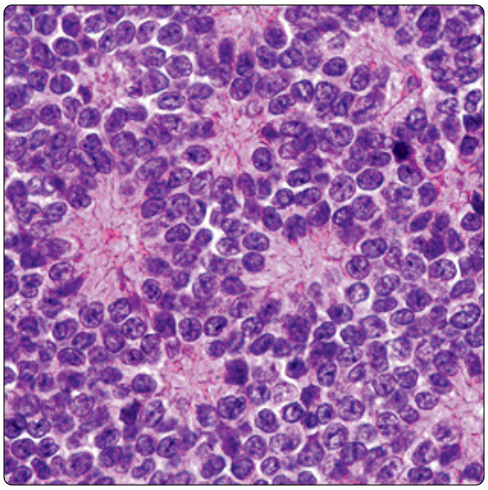


**(Left)** *Very high-power view of Ewing sarcoma shows that the neoplastic cells are somewhat cohesive and have eosinophilic cytoplasm and nuclei with finely dispersed chromatin with small nucleoli. The intracytoplasmic vacuoles represent pockets of glycogen* ➡. **(Right)** *Touch print of Ewing sarcoma shows sheets of primitive cells that have oval nuclei that have fine chromatin and pale basophilic cytoplasm. Notice the difference in size between the tumor cells and red blood cells.*

### Numerous Rosettes

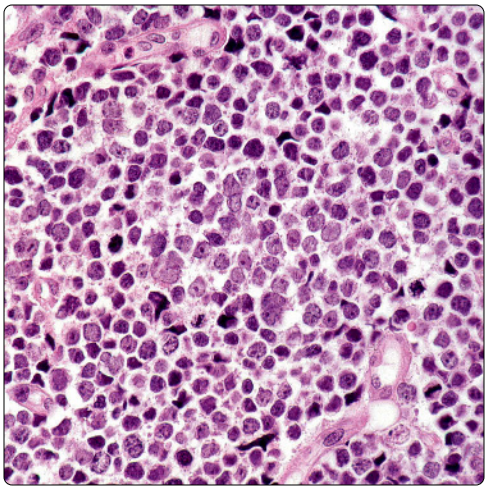


### Homer Wright Rosettes

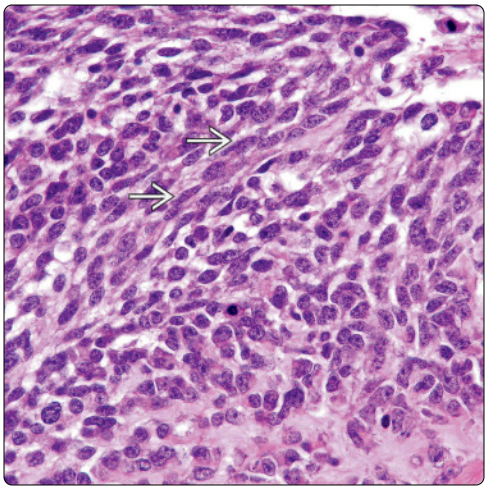


**(Left)** *This Ewing sarcoma shows prominent Homer Wright rosette formations* ➡, *which are composed of intertwining cytoplasmic processes. Previously, tumors with this morphology were classified as primitive neuroectodermal tumor (PNET).* **(Right)** *High-power view shows Homer Wright rosettes in Ewing sarcoma/PNET. Rosettes are formed by intertwining eosinophilic cytoplasmic processes. The nuclei are regular in size and shape and have finely dispersed chromatin.*

### Large Cells With Coarse Chromatin



### Spindling of Tumor Cells

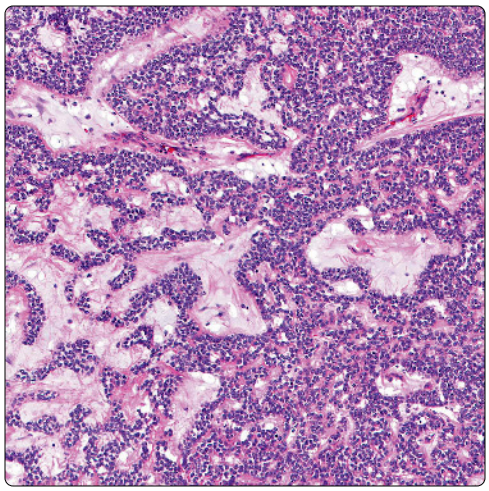


**(Left)** *This Ewing sarcoma is composed of cells that are larger than usually seen in this type of tumor and have more coarse chromatin and prominent nucleoli. Tumors with this morphology have been classified in the past as large cell variant or atypical Ewing sarcoma.* **(Right)** *Ewing sarcoma with some spindle-shaped neoplastic cells* ➡ *is reminiscent of spindle cell sarcomas, such as synovial sarcoma. This morphology is unusual for Ewing sarcoma and can cause diagnostic problems.*

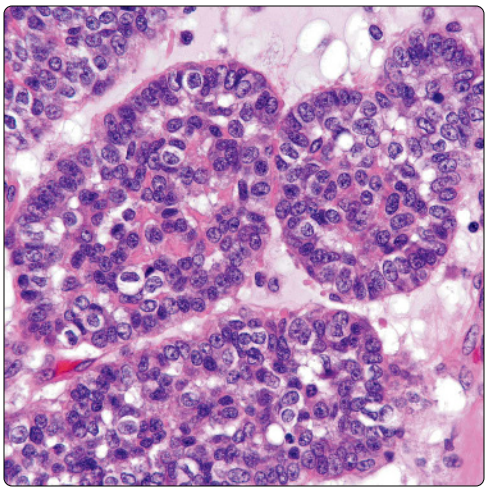


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### Cords of Tumor Cells

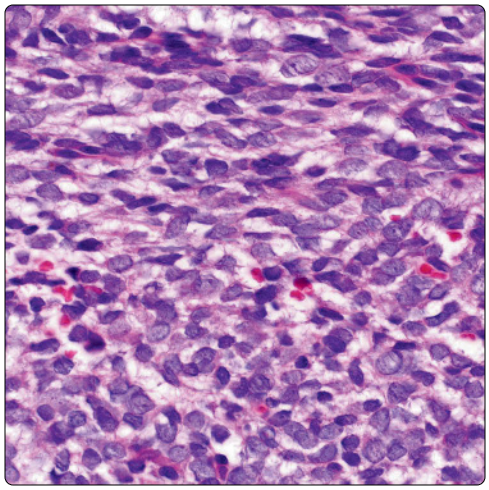


### Palisading of Tumor Cells

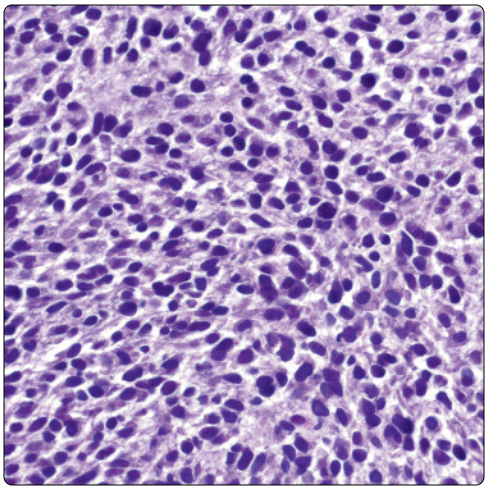


**(Left)** *This adamantinoma-like Ewing sarcoma is characterized by interconnecting nests and cords of neoplastic cells embedded in a collagenous or loose stroma. The islands of tumor cells impart an epithelial appearance.* **(Right)** *High-power view of the adamantinoma-like Ewing sarcoma demonstrates the pronounced peripheral palisading typically seen in this variant. The groups of cells are surrounded by loose connective tissue and mimic adamantinoma of bone and basaloid carcinoma.*

### Round and Spindle Cells

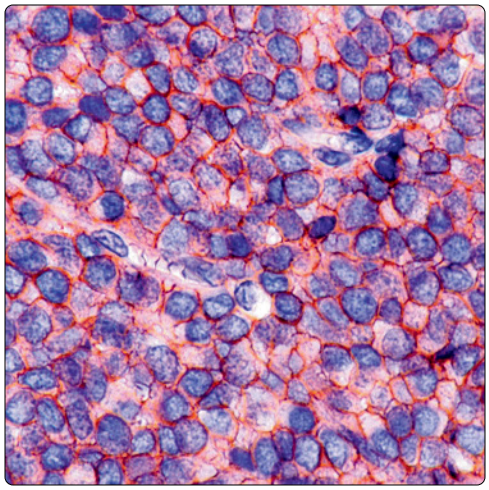


### Heterogeneous Tumor Cells

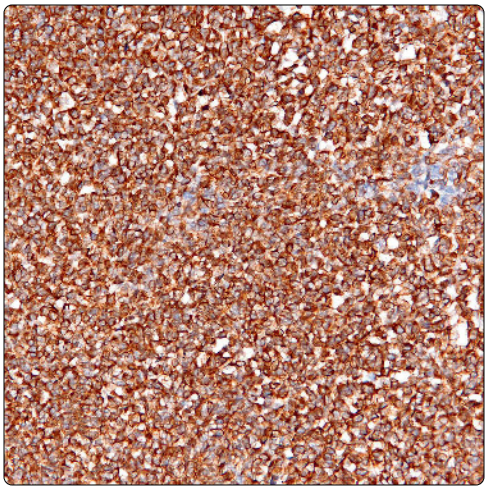


**(Left)** *This tumor has a BCOR-CCNB3 and is composed of the sheets of small round cells and fascicles of short spindle cells. The nuclei have fine chromatin.* **(Right)** *This sarcoma has a CIC-DUX4 fusion and is composed of a heterogenous population of tumor cells. The tumors vary in size and range from round to oval in shape. The nuclei are hyperchromatic.*

### Membranous Staining for CD99



### Strong Staining for Keratin

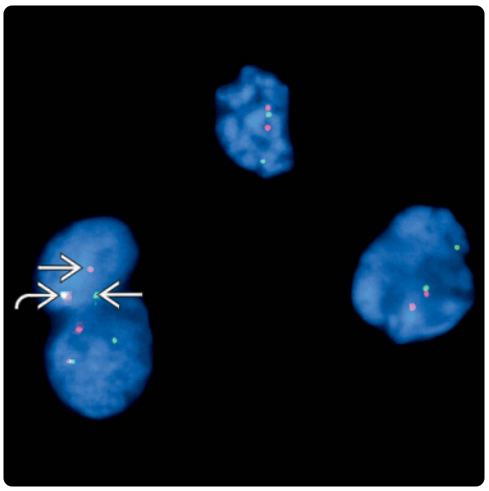


**(Left)** *Ewing sarcoma stained for CD99 shows a membranous pattern of staining. The majority of Ewing sarcomas stain for CD99; other diagnoses should be considered if negative. Other tumors, like lymphoblastic lymphoma, show a similar pattern of staining.* **(Right)** *Ewing sarcoma shows strong and diffuse cytoplasmic staining for cytokeratin. Keratin staining occurs in ~ 20% of Ewing sarcomas. Some of cells possess intracytoplasmic tonofilaments and intercellular junctions.*

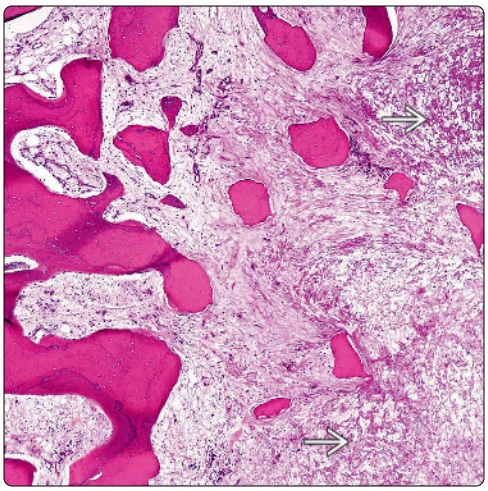


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**Rearrangement of *EWSR1***

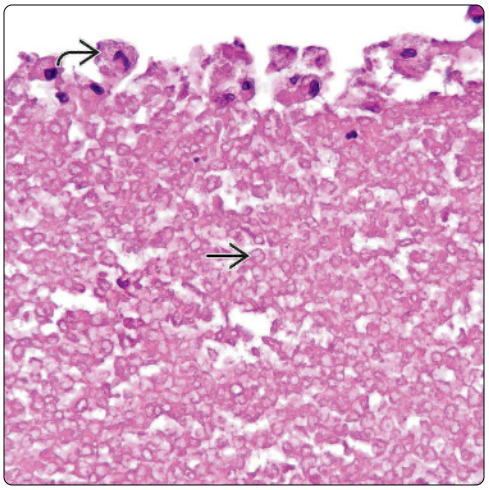


**Treatment Effect**

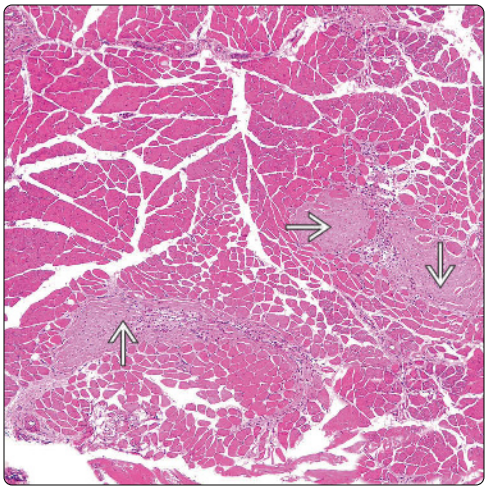


**(Left)** *FISH using a break-apart probe for Ewing sarcoma shows rearrangement of the gene on chromosome 22, proven by the separation of the green and red signals. The juxtaposition of the signal (sometimes appearing yellow) is a normal Ewing sarcoma locus.* **(Right)** *A resection specimen from a chemotherapy-treated Ewing sarcoma shows clusters of necrotic tumor cells and areas where the tumor cells have dropped out and replaced by fibrous tissue.*

**Ghost Tumor Cells**

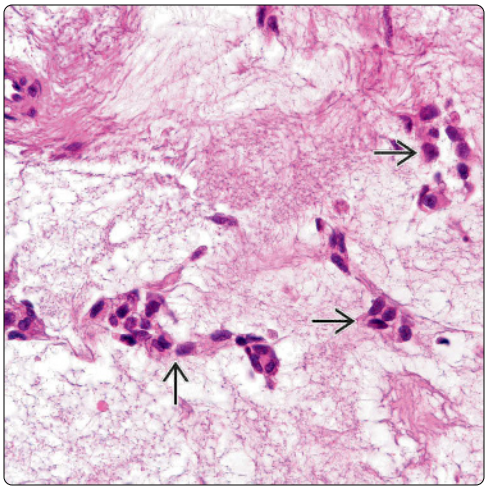


**Residual Islands of Tumor in Muscle**

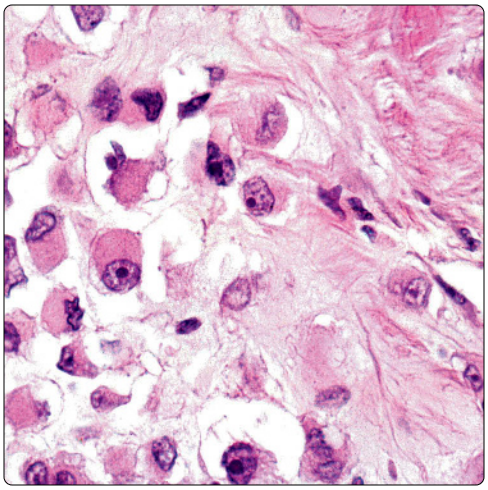


**(Left)** *A Ewing sarcoma that has been treated with chemotherapy shows necrotic ghosts cells being phagocytized by adjacent histiocytes. The histiocytes have foamy cytoplasm caused by digested cell membranes of the tumor cells.* **(Right)** *A resection specimen from a patient with Ewing sarcoma treated with chemotherapy shows small, separate, nodular aggregates of treated tumor in the skeletal muscle away from the main tumor mass, which arose in adjacent bone.*

**Resistant Nests of Tumor Cells**



**Ganglion-Like Cells**



**(Left)** *Ewing sarcoma in a patient after chemotherapy shows that most of the tumor has undergone necrosis and has been replaced by loose fibrous tissue. Scattered groups of chemotherapy-resistant, histologically intact tumor cells are still present, and they may be resistant to the drugs.* **(Right)** *Rarely, Ewing sarcomas/PNETs treated with chemotherapy show differentiation of the tumor cells toward mature ganglion cells. These "matured" cells have eccentric nuclei with prominent nucleoli and abundant pink cytoplasm.*

# Melanotic Neuroectodermal Tumor

KEY FACTS

## TERMINOLOGY

- Rare neoplasm arising in infants, composed of 2 populations of cells: Neuroblastic and pigmented (melanocytic)

## CLINICAL ISSUES

- Majority diagnosed during 1st year of life, usually in head and neck region
- Overall local recurrence rates range from 10-15%
- Arise in head and neck region, usually anterior portion of maxilla
- Surgical removal
- Rapidly growing, painless pigmented mass
- When arising in maxilla, may cause anterior protrusion of upper lip and interfere with feeding
- More common in females

## IMAGING

- Osteolytic lesion that displaces teeth and tooth buds

## MACROSCOPIC

- Firm, solid, tan-gray to black cut surface

## MICROSCOPIC

- Tumor is composed of 2 populations of cells
- Larger, more epithelioid-appearing cells are arranged in pseudoglandular, glandular, or tubular structures and show epithelial and melanocytic differentiation
- Nests of cells are surrounded by external basal lamina
- Large cells have abundant melanosomes in different stages of development, numerous mitochondria, free ribosomes, and intercellular junctions

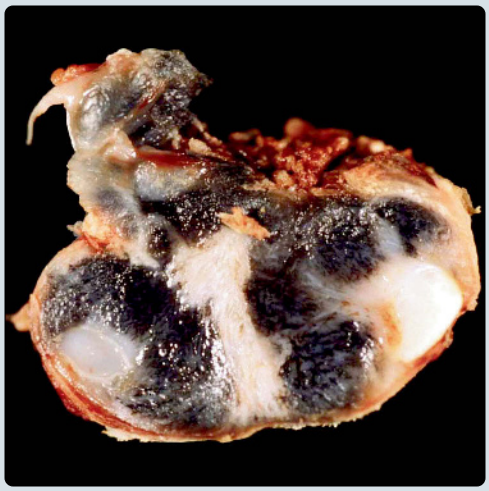
## ANCILLARY TESTS

- Larger cells show epithelial and melanocytic differentiation: Positive for keratin and HMB-45

## DIAGNOSTIC CHECKLIST

- Tumor with epithelial cells containing melanin pigment; think melanotic neuroectodermal tumor

**Anterior Maxilla**

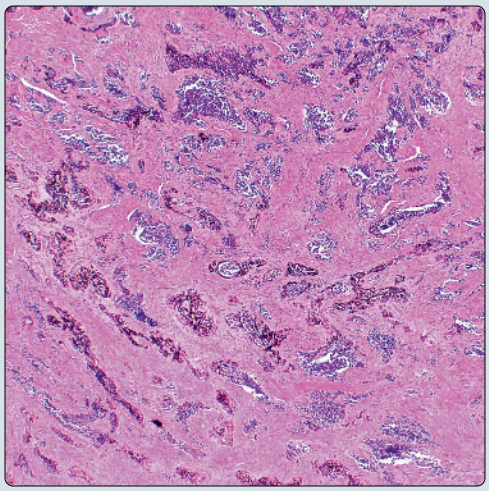


**Maxilla**

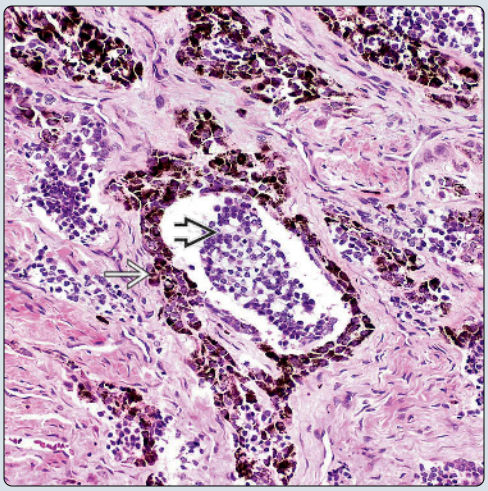


**(Left)** *This gross photograph of a melanotic neuroectodermal tumor shows a well-circumscribed tumor with the characteristic black and gray cut surface. Two teeth are present.* **(Right)** *Axial CT through the mandible of an infant shows multifocal lytic lesions with intervening bone formation. Some of the tumor nodules have broken through the cortex to produce a soft tissue mass.*

**Nested Growth Pattern**



**Populations of Cells**



**(Left)** *A low-power view of a melanotic neuroectodermal tumor demonstrates the typical nested growth pattern of the neoplastic cells separated by a prominent fibrous stroma.* **(Right)** *A high-power view of melanotic neuroectodermal tumor shows the 2 populations of cells: The large epithelioid cells with prominent intracytoplasmic melanin pigment ⇒ and nests of small, round, nonpigmented cells ⇨.*



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## TERMINOLOGY

### Synonyms

- Melanotic ameloblastoma, pigmented ameloblastoma, melanoameloblastoma, melanotic progonoma, retinal anlage tumor, congenital melanocarcinoma, retinoblastic teratoma
  - Different terms reflect uncertain histogenesis of this neoplasm, although it is currently considered to be of neural crest origin

### Definitions

- Rare neoplasm arising in infants, composed of 2 population of cells: Neuroblastic and pigmented
- Based on morphology and antigen profile, melanotic neuroectodermal tumor of infancy may represent dysembryogenetic neoplasm that recapitulates retina at 5 weeks of gestation

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Very rare tumor
- Age
  - Majority diagnosed during 1st year of life; 95% of patients are < 1 year old at time of diagnosis
- Sex
  - More common in females

### Site

- Arise in head and neck region, usually anterior portion of maxilla, also arise in mandible
- Other locations include brain, intracranial dura, and testes

### Presentation

- Rapidly growing, painless pigmented mass
- When arising in maxilla, may cause anterior protrusion of upper lip and interfere with feeding
- Some tumors have been shown to secrete vanillylmandelic acid

### Treatment

- Surgical removal

### Prognosis

- Overall local recurrence rates range from 10-15%; metastases occur in < 5% of cases
- Histologically, it is not possible to predict which tumors will metastasize; exception is rare case with features of neuroblastoma

## IMAGING

### Radiographic Findings

- Osteolytic lesion that displaces teeth and tooth buds

### MR Findings

- Mass is hyperintense to muscles and tongue on both T1- and T2-weighted images

### CT Findings

- CT shows well-demarcated and expansile tumor with surrounding thin shell of bone

## MACROSCOPIC

### General Features

- Firm, solid, tan-gray to black cut surface

## MICROSCOPIC

### Histologic Features

- Tumor is composed of 2 populations of cells that are embedded in fibrous stroma
- Larger, more epithelioid-appearing cells are arranged in pseudoglandular, glandular, or tubular structures
  - These cells have abundant eosinophilic cytoplasm and many contain dark brown melanin pigment
- Epithelioid cells frequently surround solid nests of smaller cells that have scant cytoplasm
  - Smaller cells are similar in appearance to lymphocytes and occasionally also contain cytoplasmic pigment
- Some cells have tapering eosinophilic cytoplasm suggestive of neuroblastic differentiation

### Ultrastructural Features

- Nests of cells are surrounded by external basal lamina
- Larger cells contain abundant melanosomes in different stages of development, numerous mitochondria, free ribosomes, and are joined to one another by numerous intercellular junctions
- Smaller cells are more primitive; nuclei are slightly irregular in size and shape and have clumped chromatin

## ANCILLARY TESTS

### Immunohistochemistry

- Larger cells show epithelial and melanocytic differentiation: Positive for keratin and HMB-45
- Small cells express neuroendocrine markers
- Rare tumors stain for desmin, muscle actin, and glial fibrillary acidic protein
- Both cell types usually negative for S100 protein

## DIFFERENTIAL DIAGNOSIS

### Alveolar Rhabdomyosarcoma

- Can mimic melanotic neuroectodermal tumor on low power; frequently contains multinucleated giant cells and stains for skeletal muscle markers

### Ewing Sarcoma/Primitive Neuroectodermal Tumor

- Does not contain dual population of cells

### Neuroblastoma

- Lacks 2 populations of cells; diffusely positive for neuroendocrine markers and lacks keratin positivity

### Melanoma

- Mucosal melanoma is extremely rare in children and does not show dual population of cells; negative for epithelial markers

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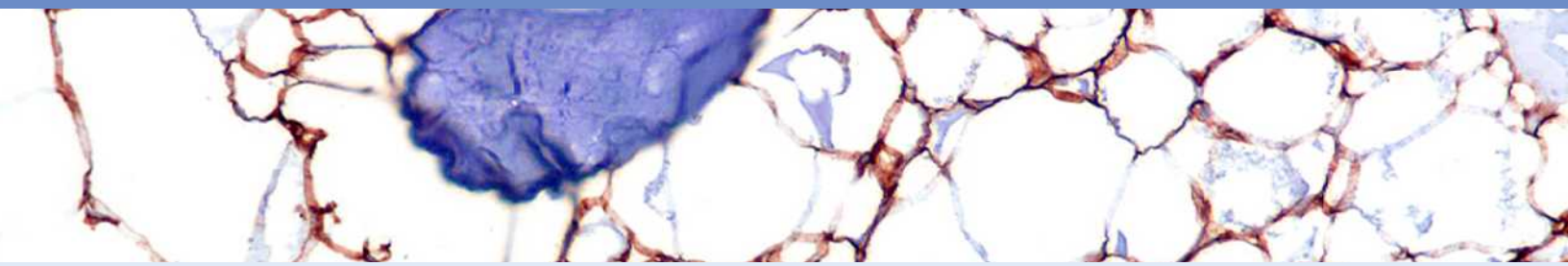
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SECTION 8

# Notochordal Tumors




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# Ecchordosis

KEY FACTS

## TERMINOLOGY

- Synonym: Ecchordosis physaliphora

## ETIOLOGY/PATHOGENESIS

- Proliferation of remnant of fetal notochord

## CLINICAL ISSUES

- Incidence 0.38%
- Typical intracranial location is retroclival
- Generally asymptomatic
- No therapy is required
- Main importance is its distinction from chordoma, particularly rare extraosseous chordoma

## IMAGING

- More homogeneously hyperintense than CSF on T2-weighted images
- No enhancement seen after contrast
- Osseous stalk is considered hallmark of ecchordosis

## MACROSCOPIC

- Well-circumscribed, round to oval, gelatinous nodule

## MICROSCOPIC

- Similar to chordoma
- Large cells arranged in cords or clusters
- Varying amounts of basophilic myxoid matrix
- Nuclei are round to oval and do not exhibit significant nuclear atypia, mitotic activity, or necrosis

## TOP DIFFERENTIAL DIAGNOSES

- Chordoma
- Benign notochordal cell tumor

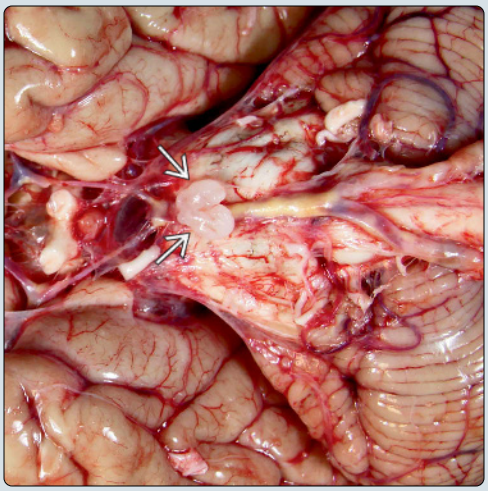
## DIAGNOSTIC CHECKLIST

- Histologically, on needle biopsy, ecchordosis may be indistinguishable from chordoma

**MR of Ecchordosis**

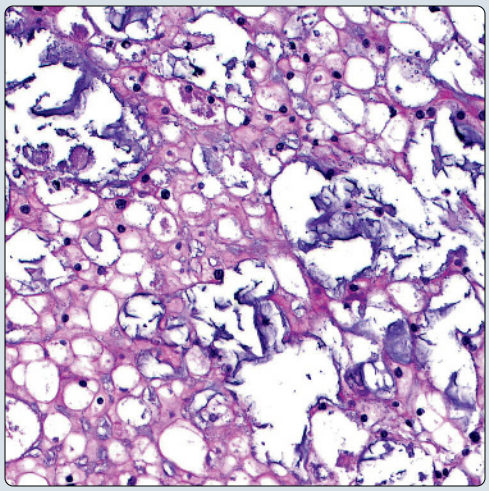


**Ecchordosis Identified at Autopsy**

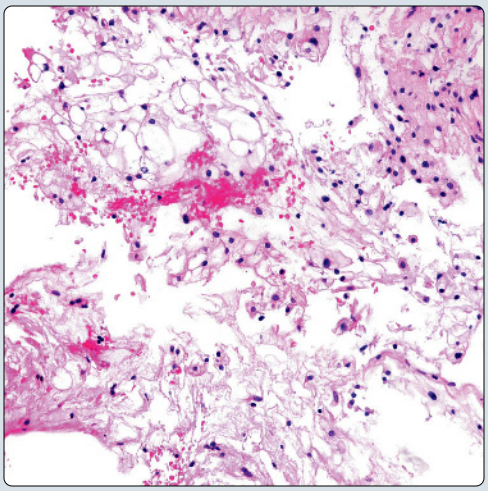


**(Left)** *Sagittal T1 MR in an asymptomatic patient shows a hypointense mass in the prepontine cistern. The lesion deforms the ventral surface of the pons. (Right) Ecchordosis identified at autopsy is shown. The lesion is ventral to the pons, overlying the basilar artery. The lesion is well circumscribed, grey-white, and gelatinous. In this patient, ecchordosis was an incidental finding and clinically asymptomatic.*

**Notochordal Cells With Mucoid Stroma**



**Chordoma Mimicking Ecchordosis**



**(Left)** *Photomicrograph of ecchordosis shows large cohesive epithelioid cells. The cells are separated by basophilic mucoid stroma.* **(Right)** *This biopsy is from a lesion ventral to the pons. Although this notochordal lesion lacked cellular atypia, the destructive intraosseous component noted on imaging supports a diagnosis of a chordoma. Based solely on histologic grounds, it may be difficult to distinguish ecchordosis from chordoma.*



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## TERMINOLOGY

### Synonyms

- Ecchordosis physaliphora

## ETIOLOGY/PATHOGENESIS

### Developmental Anomaly

- Remnant of fetal notochord with limited growth
  - Notochord 1st appears in humans around weeks 2-3 of gestation and develops into rod-like midline structure
  - By birth, notochord becomes sequestered in central portion of intervertebral disc
  - By end of 1st decade of life or sooner, there is complete dissolution of all notochordal cells
  - Rarely, these notochordal remnants may persist into adulthood
    - In nucleus pulposus of intervertebral disc
    - Proliferates in vertebral body (benign notochordal cell tumor)
    - Proliferates in soft tissue anterior to central nervous system
    - Rarely, notochordal remnants may persist as cylinder of nonossified tissue coursing vertically through center of vertebral body
  - Benign notochordal proliferations more common in ends of axial skeleton

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Identified in 6 of 1600 autopsies: Incidence 0.38%
- Age
  - Wide age distribution

### Site

- Along midline of craniospinal axis, from dorsum sellae to sacrococcygeal region
- Typical intracranial location is retroclival

### Presentation

- Generally asymptomatic
  - Involvement of brainstem or cranial nerves should suggest diagnosis of chordoma
- Usually diagnosed on CT obtained for nonspecific symptoms, such as headache
- Very rarely, patients have had fatal pontine hemorrhage or CSF fistula

### Treatment

- No therapy is required
  - Symptomatic cases may require surgery

### Prognosis

- Ecchordosis is incidentally detected finding of no clinical significance
- Main importance is distinction from chordoma, particularly rare extraosseous chordoma

## IMAGING

### MR Findings

- Minimally hyperintense to CSF on T1-weighted images
- More homogeneously hyperintense than CSF on T2-weighted images

### CT Findings

- Bony destruction is not seen
- No enhancement seen after contrast
- Osseous stalk arising from clivus is often present on CT
  - Osseous stalk is considered hallmark of ecchordosis

## MACROSCOPIC

### General Features

- Well-circumscribed, round to oval, gelatinous nodule

### Size

- Few millimeters to 2 cm

## MICROSCOPIC

### Histologic Features

- Large cells arranged in cords or clusters
  - Resembles chordoma
- Varying amounts of basophilic myxoid matrix
- Cells show abundant eosinophilic to clear multivacuolated cytoplasm
- Nuclei are round to oval and do not exhibit significant nuclear atypia, mitotic activity, or necrosis

## ANCILLARY TESTS

### Immunohistochemistry

- Positive for cytokeratin, S100 protein, and brachyury
- Immunohistochemistry does not distinguish between ecchordosis, chordoma, and notochordal vestiges

## DIFFERENTIAL DIAGNOSIS

### Chordoma

- Arises extradurally and shows osseous destruction
- Enhances with contrast
- Cytologically atypia and infiltrate preexisting bone

### Benign Notochordal Cell Tumor

- Intraosseous vertebral lesion that typically does not extend into soft tissue
- Lacks myxoid stroma

### Notochordal Remnants in Intervertebral Discs

- Located in intervertebral disc of fetus and rarely adult
- Notochordal cells in abundant myxoid stroma

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Histologically may be indistinguishable from chordoma
- Correlation with imaging essential for distinction

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1. Amer HZ et al: Intraosseous benign notochordal cell tumor. Arch Pathol Lab Med. 134(2):283-8, 2010



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KEY FACTS

## TERMINOLOGY

- Distinctive, intraosseous, slow-growing notochordal cell proliferation that behaves in indolent fashion

## CLINICAL ISSUES

- Asymptomatic; incidental finding
- Majority are in axial skeleton, most commonly sacrum and skull base
- Asymptomatic
- Incidental finding identified during evaluation for other medical issues
- No treatment is needed

## IMAGING

- Usually manifest as irregular area of sclerosis within vertebral body
- Solitary, occasionally multiple
- Bright on T2-weighted images
- Confined to vertebral body

- Differential diagnosis often includes hemangioma

## MACROSCOPIC

- May be small or involve most of vertebral body
- Does not demonstrate bone destruction
- Irregular contour, tan-white, and gritty

## MICROSCOPIC

- Well-delineated sheets of large polyhedral cells
- Cells have abundant clear to pale pink cytoplasm and mildly pleomorphic round nuclei containing fine or homogeneously dense chromatin
- Hyaline globules of varying size may be present in cytoplasm of cells
- Reactive bone formation
- No myxoid stroma is present

## ANCILLARY TESTS

- Same profile as chordoma
- Positive for keratin, EMA, S100, brachyury

**Multiple BNCTs**



*Coronal CT shows sclerotic lesions in the lumbar vertebral bodies adjacent to the endplates that are focally irregular. Margins are somewhat irregular but fairly well defined.*

**Sclerotic BNCTs**



*This adjacent lumbar vertebrae contains benign notochordal cell tumors (BNCTs) that are oval, irregular, tan-white lesions within the medullary cavities. The tan-white component correlates with reactive bone.*



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## TERMINOLOGY

### Abbreviations

- Benign notochordal cell tumor (BNCT)

### Synonyms

- Giant notochordal cell rest
- Giant notochordal hamartoma

### Definitions

- Distinctive, intraosseous, slow-growing notochordal cell proliferation that behaves in indolent fashion

## ETIOLOGY/PATHOGENESIS

### Unknown

- Notochordal cell origin

## CLINICAL ISSUES

### Site

- Almost all are located within axial skeleton
  - Sacrum: 29.5%
  - Coccyx: 17.5%
  - Cervical spine: 17.5%
  - Lumbar vertebrae: 11.5%
- Distribution in axial skeleton is similar to that of chordoma
- Very rare cases arising outside axial skeleton have been described
  - Rarely intraosseous BNCT can extend through defect in cortex and show limited involvement of soft tissue
    - Reported in skull base and sacrum

### Presentation

- Asymptomatic
- Incidental finding
- Sclerotic lesion that is discovered on radiographic images usually performed for other reasons

### Treatment

- No treatment is needed
  - Patient should be followed with imaging studies to exclude incipient chordoma or rare progression into chordoma

### Prognosis

- Excellent
  - Imaging studies have shown that BNCT may enlarge very slowly over many years
- BNCT is thought to be possible precursor lesion of chordoma
  - Evidence supporting this hypothesis is that BNCT can be seen adjacent to chordoma
    - Distribution of both BNCT and chordoma in axial skeleton is similar
    - Transformation of BNCT into chordoma has been documented
- BNCT should not be treated to prevent progression into chordoma as risk is extremely low

## IMAGING

### Radiographic Findings

- Solitary
- Occasionally multiple
- Usually manifests as irregular area of sclerosis within vertebral body
  - Mimics hemangioma radiographically
    - Some lesions diagnosed radiographically as hemangioma are probably BNCTs

### MR Findings

- Bright or isointense on T2-weighted images
- Usually confined to vertebral body
  - Can have very small extraosseous component
  - If there is extraosseous component or any lytic areas, then possibility of chordoma arising in association with BNCT has to be considered

### CT Findings

- Radiodense with irregular configuration
- Usually confined to vertebral body; rarely cortical defect present with extension into soft tissue

## MACROSCOPIC

### General Features

- Sclerotic
  - May be small or may involve substantial portions of vertebral body
  - Does not demonstrate bone destruction
  - No gelatinous areas
- Associated rebuttressed trabecular bone is hard and gritty and may obscure lesion

### Size

- Usually < 1 cm in diameter
  - Can rarely be several centimeters in greatest dimension and fill vertebral body

## MICROSCOPIC

### Histologic Features

- Well delineated
  - Composed of sheets of large, polyhedral epithelioid cells that have well-defined cytoplasmic membranes
  - Tumor is sharply demarcated and is surrounded by or abuts sclerotic bone trabeculae and entraps hematopoietic marrow
- Cells are large and have abundant clear to pale pink cytoplasm and mildly pleomorphic round nuclei containing fine or homogeneously dense chromatin
  - Cells with clear cytoplasm resemble adipocytes
- Some cells with pink cytoplasm contain round, intracytoplasmic hyaline globules of varying size
  - Globules are PAS(+) diastase resistant and are also present in small extracellular cystic spaces
- No mitoses are present
- No myxoid stroma is present
  - Important feature in distinguishing BNCT from chordoma
- Infrequently, lesion is located eccentrically in bone and can extend through cortex and displace periosteum, forming small soft tissue component



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## ANCILLARY TESTS

### Immunohistochemistry

- Same profile as chordoma
  - Keratin (+)
    - Staining is extensive and intense
  - S100(+)
  - Brachyury (+)
    - Brachyury is nuclear transcription factor that is very sensitive and specific for notochord and notochordal lesions
      - Does not distinguish between different types of notochordal tumors
    - Nuclear staining is relevant pattern for diagnosis
- EMA(+)

## DIFFERENTIAL DIAGNOSIS

### Chordoma

- Only reliable feature that distinguishes BNCT from chordoma aside from clinical and radiographic findings is lack of extracellular myxoid matrix in BNCT
- In contrast to chordoma, BNCTs are almost always confined to bone
- At time of diagnosis, chordoma invariably destroys bone and extends into adjacent soft tissue
  - Very rare for chordoma to be confined to bone of vertebra

### Notochordal Rest

- Identified within center of intervertebral disc, in region of nucleus pulposus, and not within bone

### Metastatic Carcinoma

- Tumor cells demonstrate significant cytologic atypia
  - They are keratin (+) like chordoma but lack expression of brachyury
- Mitoses are present
- Nests of tumor often surrounded by reactive fibrous tissue

### Normal Marrow Fat

- On small biopsy, BNCT can mimic marrow fat because they may appear of sheets of large cells with clear cytoplasm
- Although cells of BNCT can have abundant clear cytoplasm, they usually contain fine granular eosinophilic material, something that would not be seen in normal adipocytes

### Ecchordosis Physaliphora

- Lesion that is usually extraosseous and adjacent to brainstem in region of pons
- Unclear whether lesion is developmental in origin or analogous to osseous BNCT

### Clear Cell Chondrosarcoma

- May contain sheets of large clear tumor cells
- Has neoplastic cartilage as component
- Metaplastic bone is present through out tumor
- Does not stain with keratin or brachyury

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- When encountering normal marrow with what appears to be abundant fat on needle biopsy from vertebrae, always exclude possibility of BNCT
- Look carefully for myxoid stroma to exclude chordoma
- Correlate diagnosis with imaging studies

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Vaguely Sclerotic BNCT

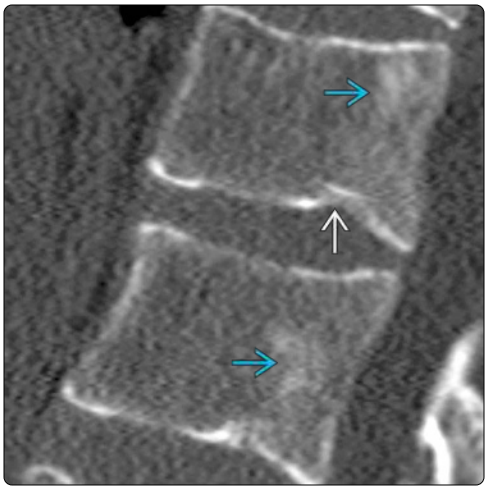


CT of BNCT



**(Left)** *Lateral radiograph demonstrates a BNCT that produces a semicircular area of sclerosis that has fairly well-defined borders in the central and posterior portion of the vertebral body. The cortex, periosteum, and other bony structures are unremarkable.* **(Right)** *Axial CT shows a BNCT located in the posterior central potion of the vertebral body. The lesion is sclerotic, irregular in contour, and has geographic margins. The cortex and periosteum are not involved.*

BNCTs



CT Scan of BNCT

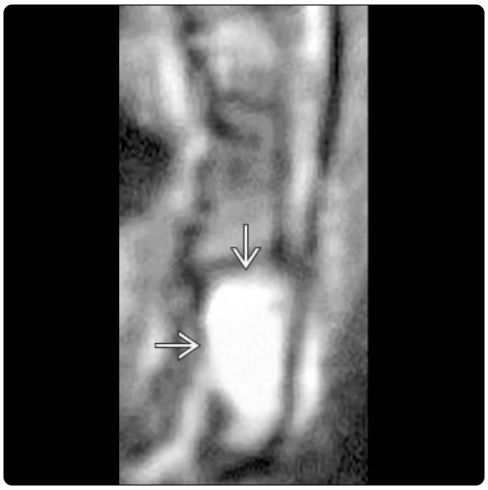


**(Left)** *Sagittal CT scan shows osteopenia with vague, sclerotic lesions in the posterior vertebral bodies. There is mild endplate compression of the superior body. Both lesions are confined to the vertebrae with no extraosseous extension.* **(Right)** *Axial CT scan shows sclerotic areas along the posterior vertebral body. The margins are fairly well demarcated.*

Chordoma Adjacent to BNCT



MR of BNCT



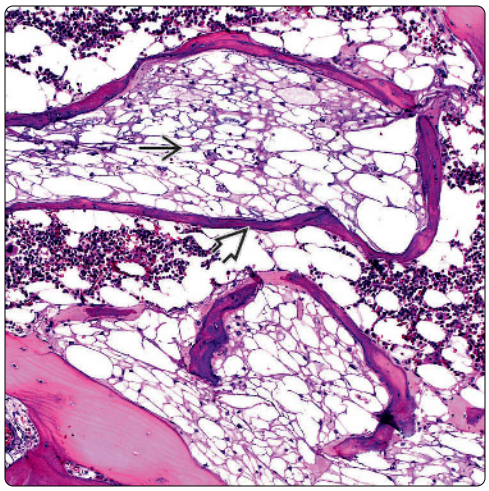
**(Left)** *Sagittal fluid-sensitive MR through the sacrococcygeal region of the spine is shown. In the distal sacrum, a large chordoma that has high signal intensity involves 2 vertebral bodies and extends into the anterior soft tissues. The distal 2 vertebral bodies each contain a BNCT that appear as irregular, intraosseous, bright signal lesions.* **(Right)** *Fluid-sensitive sagittal MR demonstrates a BNCT in the coccyx that has a bright signal and fills most of the body.*



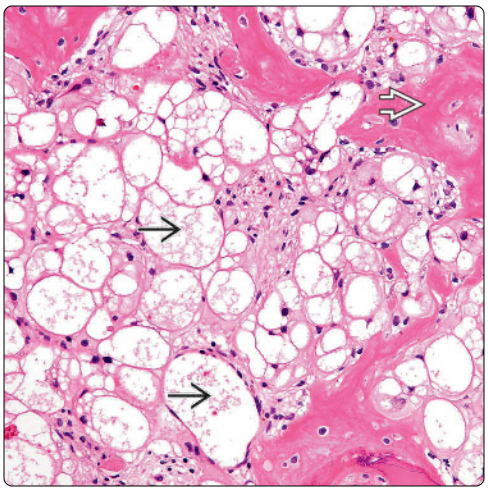
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**(Left)** *Sheets of large notochordal cells ⇨ are rimmed by trabeculae of reactive bone ⇨, which demarcate the lesional cells from the hematopoietic marrow. The notochordal cells have abundant clear cytoplasm and well-defined cell membranes.* **(Right)** *BNCT composed of aggregates of large cells with abundant cytoplasm ⇨ ranges from clear to flocculent and eosinophilic. The groups of cells are intersected by trabeculae of reactive woven bone ➡ lined by osteoblasts.*

**Well-Circumscribed BNCT**

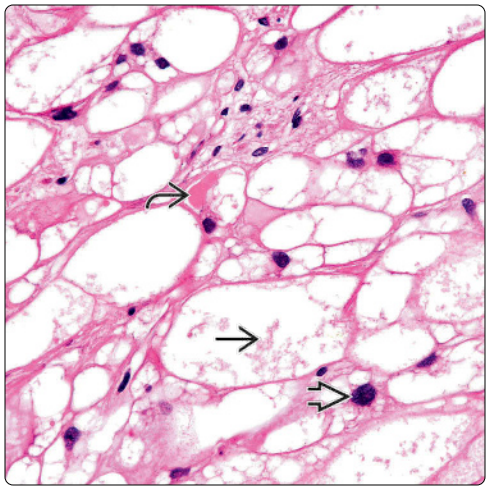


**Flocculent Eosinophilic Cytoplasm**

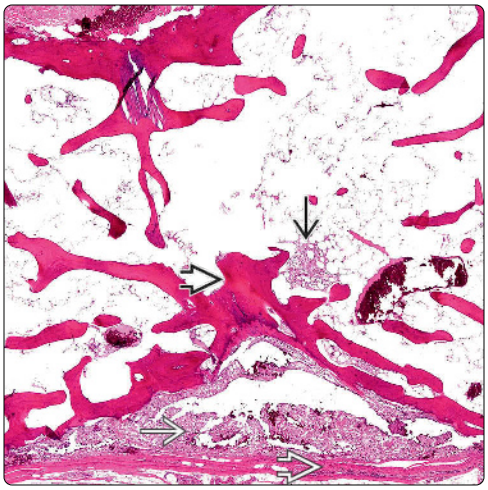


**(Left)** *The lesional cells of BNCT are large and contain abundant cytoplasm ⇨ that is vacuolated and clear or eosinophilic. The nuclei vary in size and demonstrate limited cytologic atypia ⇨. Extracellular eosinophilic globules ⇨ are present, but there is no myxoid stroma.* **(Right)** *A coccygeal vertebra contains a BNCT that involves the medullary cavity ⇨ and extends through the cortex into the soft tissues ➡ by displacing the periosteum ➡. Reactive woven bone is present ⇨.*

**Clear to Granular Eosinophilic Cytoplasm**

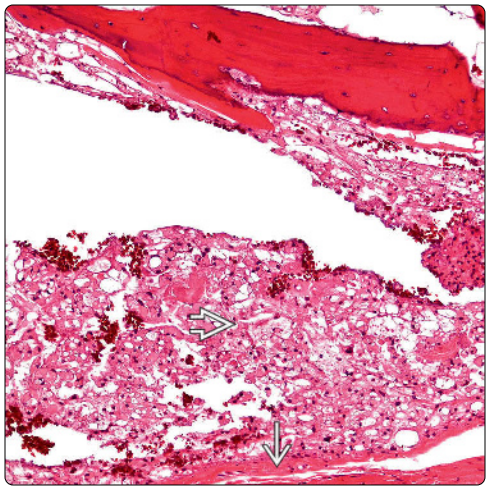


**Focal Extraosseous Extension**

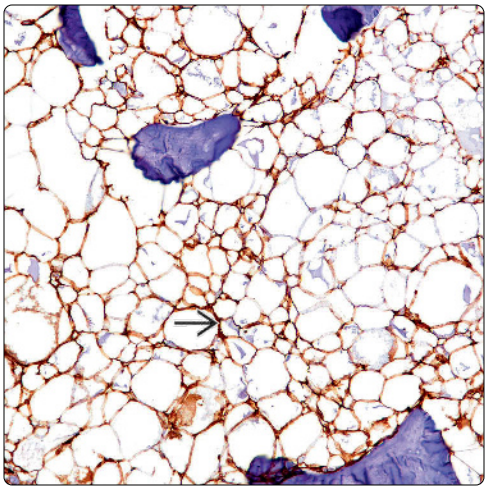


**(Left)** *Extraosseous component of BNCT is composed of sheets of large cells ➡ that have vacuolated clear and eosinophilic cytoplasm. The lesion is not destructive and is bordered peripherally by periosteum ➡. The encompassed cortex does not show any significant changes.* **(Right)** *BNCT within the medullary cavity of a coccygeal vertebra demonstrates characteristic strong expression of keratin AE1/AE3 by the lesional cells ⇨.*

**Extraosseous BNCT**



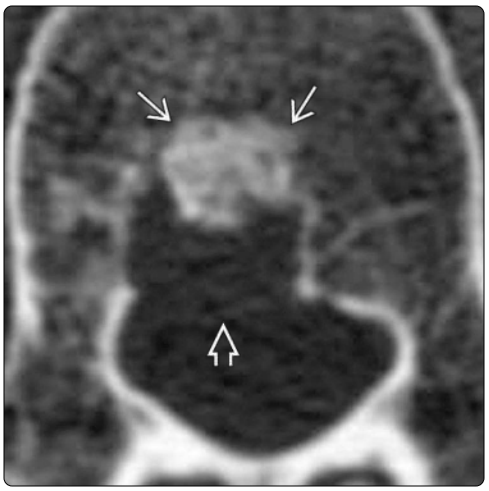
**Keratin-Positive BNCT**



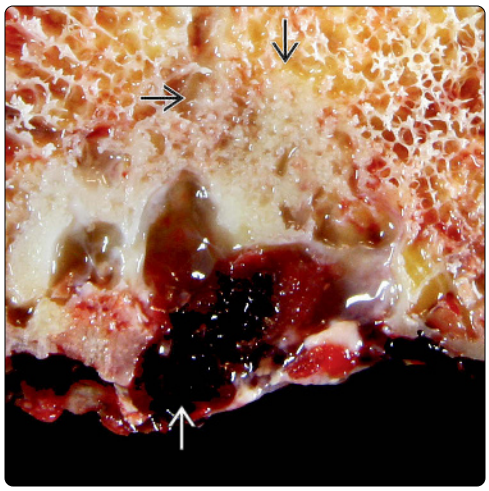


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Chordoma Arising in BNCT



Gross of Chordoma Arising in BNCT

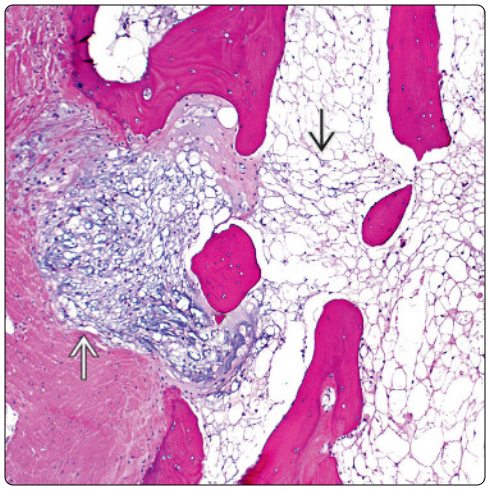


**(Left)** *Chordoma arising in a BNCT is shown. The BNCT is composed of a well-demarcated sclerotic area ➡. The adjacent chordoma is lytic and has destroyed the cortex, forming a small soft tissue component ➡.* **(Right)** *Corresponding gross image is shown. The BNCT forms a sclerotic lesion that is confined to the bone ⇨. The chordoma is hemorrhagic and myxoid and has broken through the cortex and extended into adjacent spinal canal ➡.*

MR of Chordoma Arising in BNCT

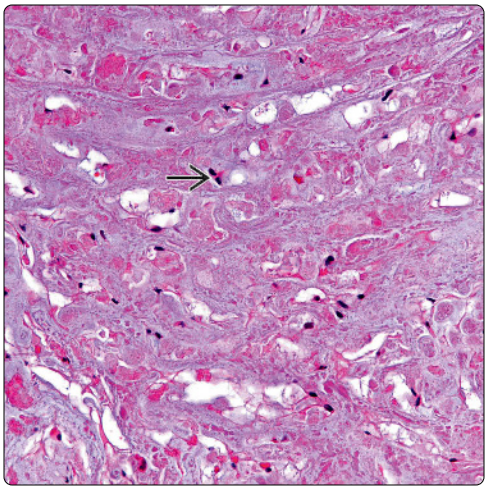


Histology of Chordoma Arising in BNCT

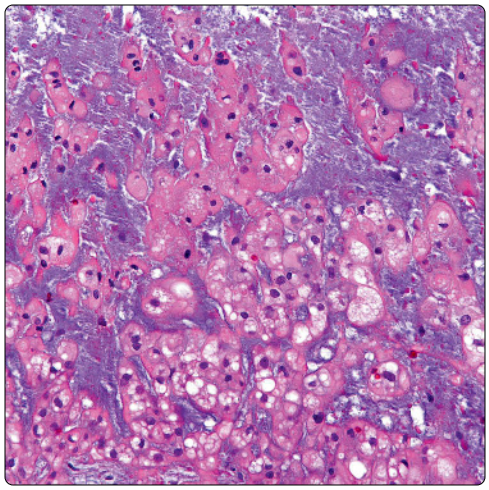


**(Left)** *Small chordoma arising in association with a BNCT is shown. The BNCT is intraosseous ⇨ and is associated with brighter component ➡ that has broken through the cortex of the distal sacrum and formed a small soft tissue mass.* **(Right)** *Light microscopy shows the lesion is predominantly composed of intraosseous BNCT made up of cells with abundant clear cytoplasm and no extracellular myxoid matrix ⇨. The chordoma has broken through the cortex ➡.*

Notochordal Remnant



Chordoma



**(Left)** *Notochordal remnant is composed of degenerative notochordal cells ⇨ in an extracellular myxoid matrix is shown. Unlike BNCT, the cells are in the area of the nucleus pulposus of the intervertebral disc and not are not intraosseous.* **(Right)** *Chordoma arising in a vertebral body. Unlike BNCT, the chordoma cells have more eosinophilic cytoplasm and are embedded in an extracellular myxoid matrix that is absent in BNCT.*



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KEY FACTS

## TERMINOLOGY

- Primary malignant tumor of bone with phenotype that recapitulates notochord and usually arises within bones of axial skeleton

## ETIOLOGY/PATHOGENESIS

- Benign notochordal cell tumor (BNCT) is thought to be precursor lesion to chordoma

## CLINICAL ISSUES

- Accounts for ~ 5% of primary malignant bone tumors; usually diagnosed during 4th-8th decades of life; restricted to axial skeleton

## IMAGING

- Destructive and lytic and invariably extends into soft tissues forming sizable mass

## MACROSCOPIC

- Soft, tan-gray, gelatinous, and lobulated; well delineated from surrounding tissues; dedifferentiated component is solid and fish flesh-like in appearance; poorly differentiated lacks myxoid areas and can have areas of necrosis

## MICROSCOPIC

- Histologically, chordoma is classified into conventional chordoma, chondroid chordoma, and dedifferentiated chordoma
  - Chondroid chordoma can mimic chondrosarcoma
  - Dedifferentiated chordomas contain high-grade sarcomatous areas and have worst prognosis
- Poorly differentiated chordoma is cellular, sometimes rhabdoid, atypical, mitotically active without extracellular matrix and can have areas of necrosis

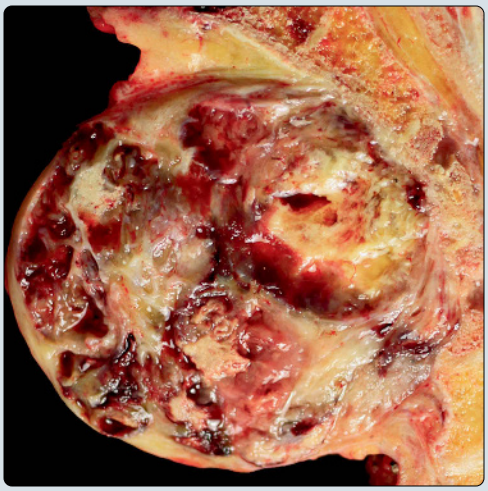
## TOP DIFFERENTIAL DIAGNOSES

- Metastatic adenocarcinoma, chondrosarcoma, BNCT, atypical teratoid rhabdoid tumor

**Large Sacral Chordoma**

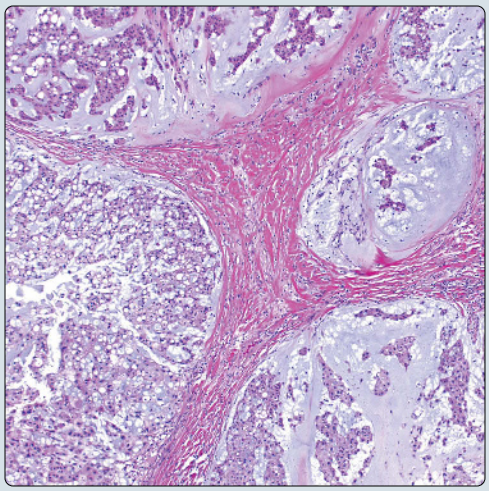


**Sacral Chordoma**

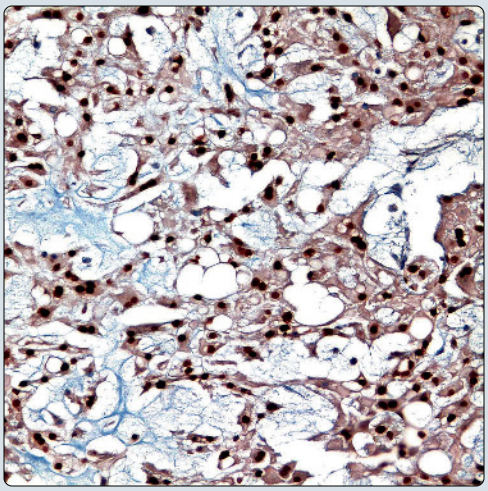


**(Left)** *Classic appearance of a sacral chordoma is shown. The tumor involves the distal sacrum and forms a large, well-demarcated anterior soft tissue mass and a much smaller posterior soft tissue mass.* **(Right)** *Corresponding resection specimen shows a large, gelatinous, yellow, and hemorrhagic tumor that arises in the sacrum and has formed a large anterior soft tissue mass that is surrounded by a thin fibrous capsule.*

**Conventional Chordoma**



**Brachyury Stain in Conventional Chordoma**



**(Left)** *Classic appearance of a conventional chordoma is shown. The tumor has a lobulated growth pattern with fibrous septa. The tumor cells have eosinophilic cytoplasm, are cohesive, and some have bubbly cytoplasm (so-called physaliphorous cells). There is extensive extracellular myxoid matrix.* **(Right)** *Chordoma is one of the very few tumors that express T-brachyury, a nuclear transcription factor found in notochord and tumors that have a notochordal phenotype. A positive reaction is evidence of strong nuclear staining.*



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## TERMINOLOGY

### Definitions

- Primary malignant tumor of bone with phenotype that recapitulates notochord and usually arises within bones of axial skeleton
- Chondroid chordoma: Tumor with areas of conventional chordoma and regions resembling low-grade, hyaline-type chondrosarcoma
- Dedifferentiated chordoma contains chordoma juxtaposed to high-grade undifferentiated sarcoma

## ETIOLOGY/PATHOGENESIS

### Neoplastic

- Benign notochordal cell tumor (BNCT) is thought to be precursor lesion to chordoma
- Variety of genetic abnormalities can be identified in sporadic and familial tumors
  - Familial tumors have been associated with upregulation of T-brachyury (nuclear transcription factor)
- There appears to be increased incidence of chordoma in patients with tuberous sclerosis

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Accounts for ~ 5% of primary malignant tumors of bone
- Age
  - Usually diagnosed during 4th-8th decades of life
  - Only 5% of tumors develop in patients under 20 years; tumors in children usually arise in skull base
- Sex
  - Men affected more frequently than women

### Site

- Virtually restricted to axial skeleton; rare cases reported to arise outside axial skeleton (extraaxial chordoma)
- Most (~ 50%) arise in sacrum; ~ 35% arise in skull base and 15% in mobile spine
- Chondroid chordoma usually arises in skull base; much less frequently in mobile spine and sacrococcygeal region

### Presentation

- Depends on site of origin
  - Skull base: Diplopia, headaches, cranial nerve palsies; mobile spine: Pain, neurologic symptoms; sacrum: Pain, constipation, incontinence, bladder dysfunction, erectile dysfunction

### Treatment

- Standard of care is combination of surgery and radiation therapy; no effective chemotherapy is currently available except in some poorly differentiated chordomas

### Prognosis

- Affected by tumor location, size, and resectability
- Sacral chordomas have best prognosis and longest overall survival as they can frequently be resected with negative margins
  - Local recurrences for sacrococcygeal tumors are common after incomplete excision
  - 5- and 10-year survival rates range from 60-95% and 40-60%, respectively
- In mobile spine, 5-year survival rate ~ 55% with local recurrence rate ranging from 62-75%
  - Primarily due to difficulty in achieving complete resection
  - Good local control can be obtained with combination of preoperative radiation therapy and surgery and postoperative radiation therapy
- In skull base, large tumors, female gender, and age > 40 years associated with poorer outcome
  - In series in which patients were treated with surgery and radiation, 46% developed local progression with median follow-up of 69 months
    - Others have reported 5-year local control rate of 59%
- Chondroid chordoma has same survival as conventional chordoma
- Dedifferentiated chordoma has worst prognosis of all chordomas
  - Usually rapidly fatal with systemic spread occurring in ~ 90% of cases
- Rate of metastatic spread of chordoma varies widely
  - Ranges from < 5-43% (highest for dedifferentiated chordoma)
- Common sites of dissemination include lung, skin, and bone
- Poorly differentiated chordomas usually have bad prognosis

## IMAGING

### Radiographic Findings

- Destructive and lytic
- Invariably extends into soft tissues, forming sizable, well-defined mass; may show calcifications
- In sacrum, soft tissue component is characteristically anterior; may displace rectum and extend along sacral nerve roots into sciatic notch
- Sacral tumors are notoriously difficult to see on conventional radiographs

### MR Findings

- Extremely bright on T2-weighted images; may show lobulated pattern; foci of calcification are frequently seen
- Soft tissue extent better seen

### CT Findings

- Has high water content and appears radiolucent, often with bone destruction; calcifications may be seen

## MACROSCOPIC

### General Features

- Soft, tan-gray, gelatinous, and lobulated; well delineated from surrounding tissues; dedifferentiated component is solid and fish flesh-like in appearance; poorly differentiated lacks myxoid areas and can have areas of necrosis

### Size

- Tumors in skull base are smallest and usually 2-5 cm in diameter
- Sacral tumors can be very large and usually > 10 cm



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## MICROSCOPIC

### Histologic Features

- Histologically, chordoma is classified into conventional chordoma, chondroid chordoma, dedifferentiated and poorly differentiated chordoma
- Conventional chordoma has lobular growth pattern, infiltrates marrow space, encases preexisting bony trabeculae, and usually transgresses cortex, forming well-demarcated soft tissue mass
  - Composed of large epithelioid cells arranged in cohesive nests and cords; one tumor cell may wrap around or "hug" another
  - Nuclei are of moderate size, darkly staining, and may contain small nucleoli or pseudoinclusions
  - Abundant eosinophilic cytoplasm; may contain multiple round, clear vacuoles that may harbor wisps of mucinous material
  - Intracytoplasmic vacuoles impart bubbly appearance to cytoplasm, and cells containing them are known as physaliphorous cells
    - Physaliphorous cells are not pathognomonic of chordoma, as other types of tumors may have similar-appearing cells, and some chordomas may lack them
    - In some tumors, physaliphorous cells have large single cytoplasmic vacuole that causes them to mimic adipocytes
  - Pleomorphism and spindling of tumor cells may be present in conventional chordoma
  - Mitotic activity is usually limited in conventional chordoma
    - Foci of necrosis are common, especially in larger tumors and poorly differentiated chordoma
  - Extracellular stroma is myxoid, frothy, basophilic
- Chondroid chordoma contains areas of conventional chordoma as well as regions resembling low-grade, hyaline-type chondrosarcoma
  - Chondroid regions merge with or abruptly abut surrounding conventional component
  - Chondroid areas composed of neoplastic cells distributed individually in lacunar-like spaces
    - Neoplastic cells are surrounded by solid-appearing hyalinized matrix similar in appearance to hyaline cartilage
  - Quantity of chondroid component in any individual tumor is variable
  - In some tumors, chondroid areas are so abundant that it may be difficult to distinguish tumor from chondrosarcoma
- Dedifferentiated chordoma is composed of high-grade sarcoma juxtaposed with conventional chordoma
  - Sarcoma is usually high-grade, undifferentiated pleomorphic sarcoma
  - Dedifferentiation results from ongoing cumulative mutations in conventional chordoma cells
- Poorly differentiated chordoma is cellular, sometimes rhabdoid in appearance, atypical, mitotically active without extracellular matrix and can have areas of necrosis

### Ultrastructural Features

- Neoplastic cells in conventional chordoma have villous-like surface projections, abundant cytoplasmic glycogen, and mitochondria-rough endoplasmic reticulum complexes
- Contain cytoplasmic processes that wrap around adjacent cell; cells have well-developed desmosomes, intracytoplasmic lumina, and tonofilaments

### Immunohistochemical Features

- Conventional chordoma typically expresses epithelial markers keratin and EMA
  - Includes keratins 8 and 19
- Vast majority stain for nuclear transcription factor T-brachyury
- Majority also stain with antibodies to S100 protein
- Variable numbers may also stain with antibodies to carcinoembryonic antigen and glial fibrillary acidic protein
- Immunohistochemical stain can be very helpful in distinguishing chondrosarcoma from chordoma, especially on small biopsy
  - Chondrosarcomas are negative for epithelial markers, especially keratin and brachyury
- Poorly differentiated chordomas frequently show loss of INI1

## DIFFERENTIAL DIAGNOSIS

### Metastatic Adenocarcinoma

- Mucinous adenocarcinoma can mimic chordoma on small biopsy sample
  - Immunohistochemical stains are helpful as adenocarcinomas are S100 protein and T-brachyury negative

### Chondrosarcoma

- On small biopsies, especially from skull base, it can be difficult to distinguish chordoma from myxoid chondrosarcoma
  - Immunohistochemical stains for keratin and brachyury are helpful as chondrosarcoma is negative for those markers
  - Both tumors stain for S100 protein

### Benign Notochordal Cell Tumor

- BNCT contains cells with abundant clear cytoplasm (adipocyte-like) or eosinophilic cytoplasm and has same immunohistochemical profile as chordoma
- Unlike chordoma, BNCTs are usually confined to bone and lack extracellular myxoid matrix histologically
- Radiographically, chordoma is lytic, whereas BNCT is sclerotic and does not show contrast enhancement

### Atypical Teratoid Rhabdoid Tumor

- Can histologically mimic poorly differentiated skull-based tumors; also are keratin positive and show loss of INI1, but they do not stain for brachyury

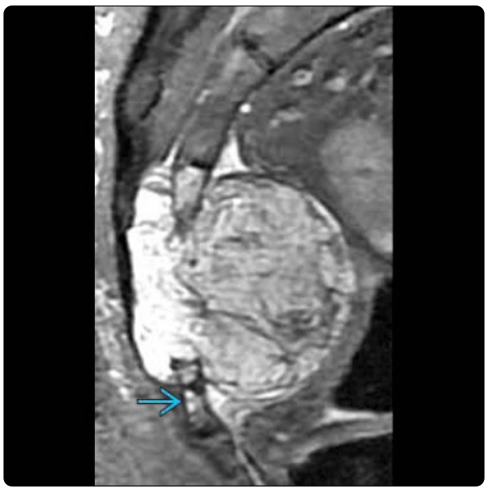
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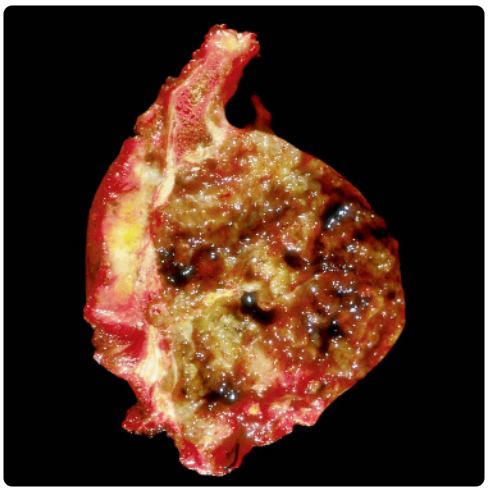


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### Chordoma and BNCT

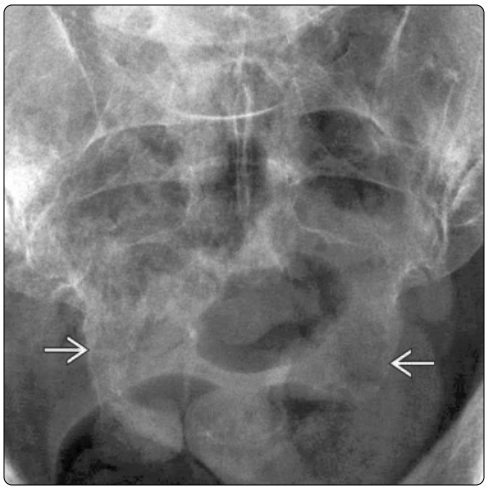


### Gelatinous Hemorrhagic Tumor

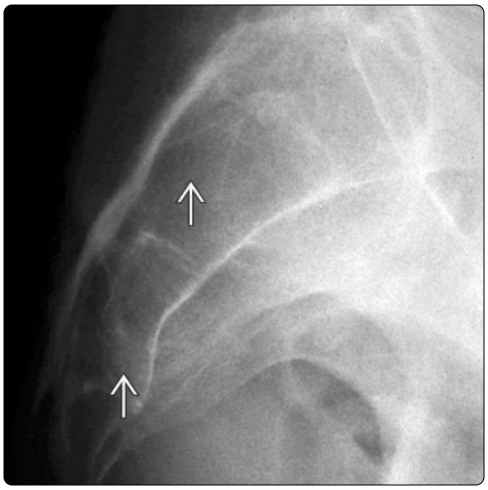


**(Left)** *Sagittal T2-weighted MR shows sacrococcygeal chordoma growing into the spinal canal and forming a large anterior soft tissue mass. Two benign notochordal cell tumors (BNCTs) with high signal intensity are in the adjacent distal vertebra.* **(Right)** *Distal sacrococcygeal chordoma arises in the vertebra and grows in an eccentric fashion into the anterior soft tissues. The gelatinous tumor is tan-gray, hemorrhagic, and has a nodular architecture.*

### Subtle Bone Destruction Radiographically



### Subtle Lytic Lesion of Sacrum

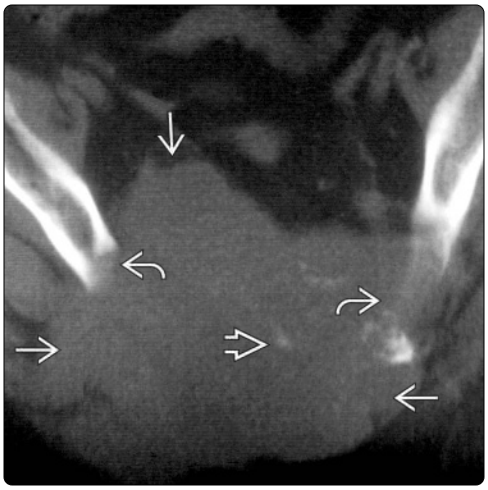


**(Left)** *Findings of bone destruction on plain radiography can be very subtle and are easily obscured by soft tissues and bowel gas. For this reason, prior to the era of advanced cross-sectional imaging, chordoma was seldom detected on imaging studies until it was quite large.* **(Right)** *Lateral radiograph of the distal sacrum and coccyx demonstrates subtle lysis of the trabecular bone of the involved vertebrae. The chordoma is easily missed on this type of imaging study.*

### Hyperintense Tumor



### Large Destructive Tumor



**(Left)** *T2-weighted sagittal MR shows a chordoma arising in the distal sacral-proximal coccygeal segment, extending proximally in the spinal canal and forming a large anterior mass.* **(Right)** *Axial CT of the pelvis shows a large, destructive chordoma of the upper sacrum destroying the cortex and forming large anterior and posterior soft tissue masses. The tumor also involves the right and left aspects of the posterior ilia and contains fine calcifications.*



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### Destructive Cervical Chordoma

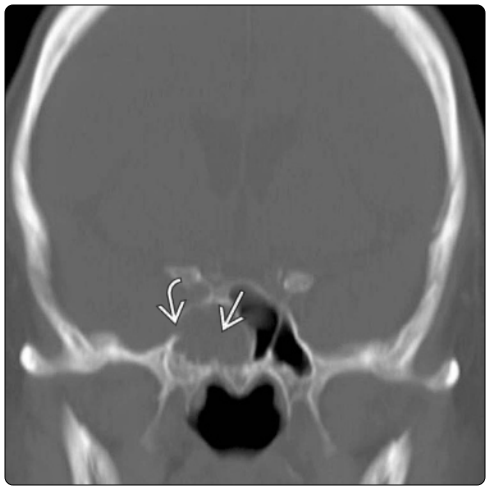


### Soft Tissue Extension



**(Left)** *Sagittal reformat of a cervical spine CT scan shows a chordoma involving the bodies of C5 and C6. A large, low-attenuation soft tissue mass is seen anteriorly, and there is a faint periosteal line that marks the presence of a posterior soft tissue mass in the spinal canal.* **(Right)** *Sagittal T2-weighted MR of the cervical spine shows the chordoma extending anteriorly into the soft tissues and posteriorly into the spinal canal.*

### Chordoma of Clivus and Sphenoid Bone

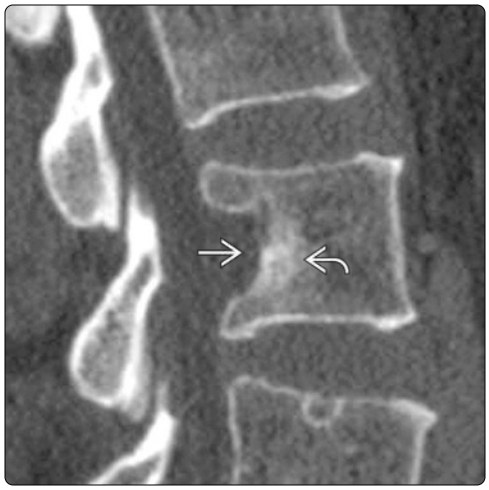


### T2-Bright Skull Base Chordoma

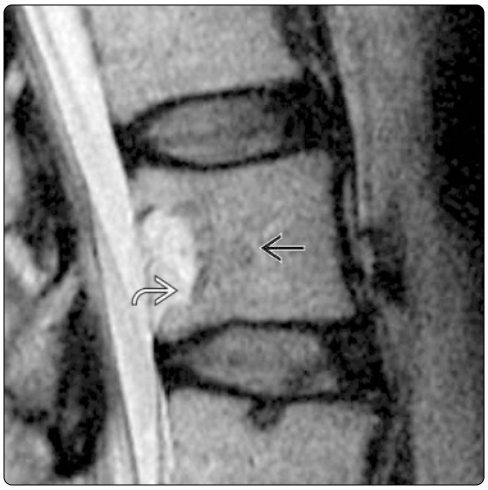


**(Left)** *Coronal reformat of a CT scan of the head shows a chordoma of the clivus extending into the sphenoid sinus. The tumor has soft tissue density and expands and erodes the bone, causing focal destruction of the bony cortex.* **(Right)** *Axial T2-weighted MR shows the chordoma as a centrally located, lobulated area of high signal. The tumor is solid and has a lobular contour with relatively well-circumscribed margins. The adjacent brain is unremarkable.*

### Chordoma Arising in BNCT



### Chordoma Arising Adjacent to BNCT



**(Left)** *Sagittal reformat of a CT scan shows a chordoma adjacent to a BNCT. The chordoma is represented by the posterior lytic area; the BNCT is seen as a region of faint sclerosis in the mid vertebra.* **(Right)** *Sagittal T2-weighted MR shows the chordoma as an elliptical area of high signal abutting the anterior spinal canal. The adjacent BNCT is subtle and seen as an area of low signal in the mid vertebra.*



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### CT of Extraaxial Chordoma

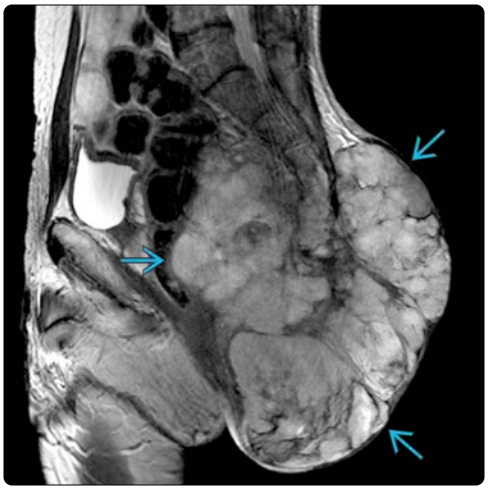


### T2-Bright Extraaxial Chordoma

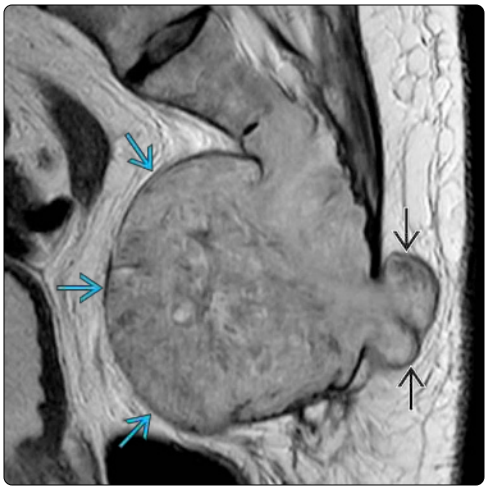


**(Left)** *Sagittal CT scan of an extraosseous chordoma shows subtle superficial erosion of the posterior vertebral cortex ⇒. The tumor mass ⇒ cannot be distinguished from the spinal canal contents.* **(Right)** *Sagittal T2-weighted MR of an extraosseous chordoma shows a large, high-signal mass ⇨ within the spinal canal extending from the top of L4 to the bottom of S1. The tumor scallops the posterior cortices of the involved vertebral bodies, which are otherwise unremarkable.*

### Giant Sacral Chordoma

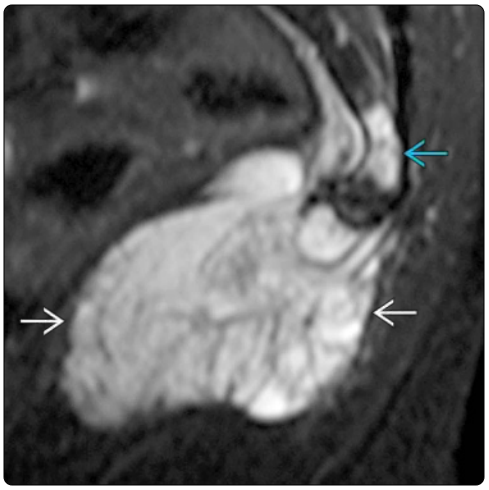


### Anterior and Soft Tissue Extension

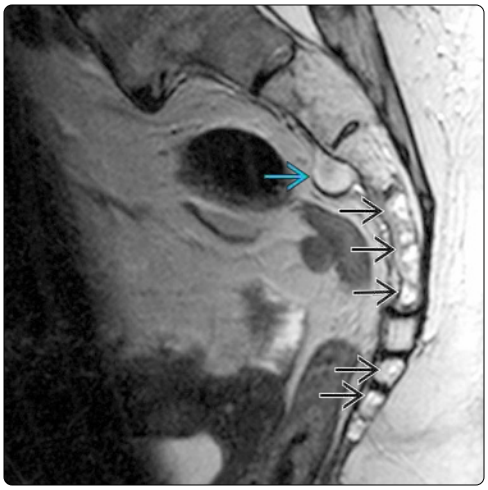


**(Left)** *Extremely large sacral chordoma ⇨ is shown. The tumor arises in the distal sacrum and forms a very large anterior, posterior, and inferior soft tissue mass.* **(Right)** *A large sacral chordoma is shown. The tumor involves a large portion of the sacrum and forms a large anterior soft tissue mass ⇨ as classically seen in sacral chordoma. The tumor also extends into the posterior soft tissues into the subcutaneous fat ⇨.*

### Chordoma Arising Adjacent to BNCT



### Chordoma and Several BNCTs

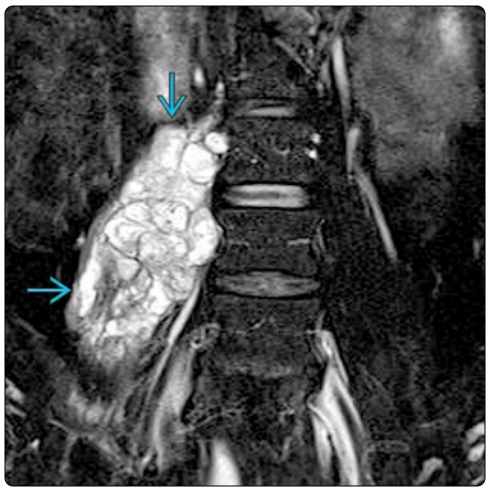


**(Left)** *MR shows a chordoma arising in association with a BNCT. The chordoma involves the distal sacrum and forms a large soft tissue mass ⇒. The proximal bright signal represents a BNCT ⇨.* **(Right)** *This sacral chordoma arises in the proximal portion of the sacrum and forms a small anterior soft tissue mass ⇨. The several hyperintense areas distal to the tumor, extending all the way to the coccyx, represent small BNCTs ⇨.*



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### Mimicking Nerve Sheath Tumor

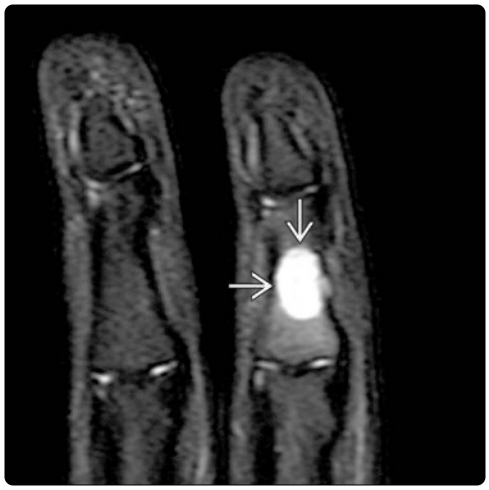


### Mimicking Nerve Sheath Tumor

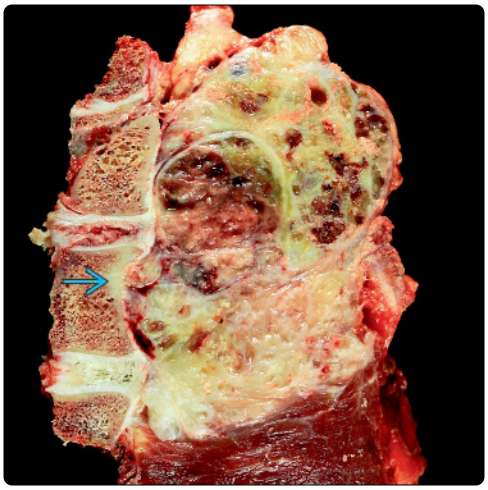


**(Left)** *This extraaxial chordoma was clinically thought to be a nerve sheath tumor. The tumor is lobulated, bright on this T2-weighted MR, and does not involve the adjacent bone ⇨.* **(Right)** *The corresponding axial MR shows that the tumor involves the neural foramina, without bone involvement, something that is classically seen in a nerve sheath tumor arising in this location.*

### Chordoma of Finger

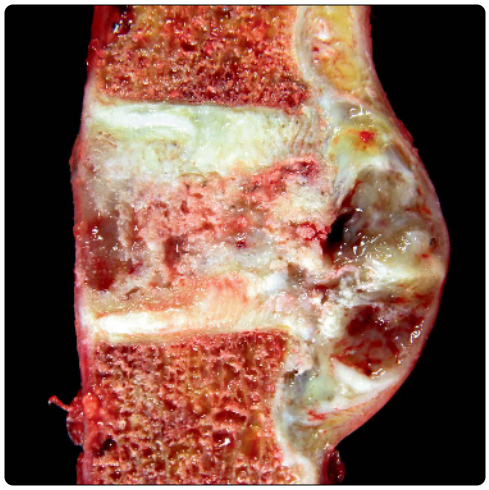


### Large Extraaxial Chordoma

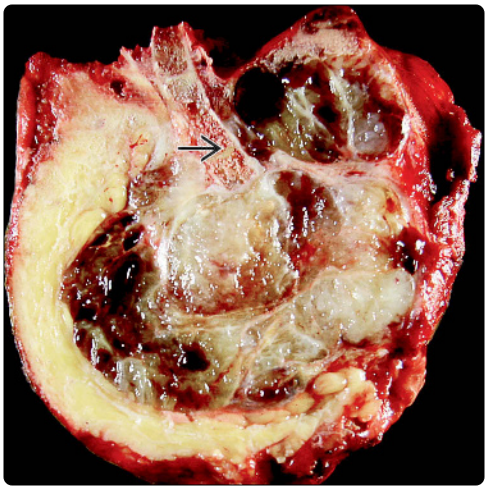


**(Left)** *A small extraaxial chordoma of the middle phalanx is shown. The tumor is bright on this T2-weighted MR and well demarcated ⇨. Histologically and immunohistochemically, it had the characteristic features of conventional chordoma.* **(Right)** *Large chordoma arising in the soft tissues adjacent to the axial spine is shown. The tumor is gelatinous, white, yellow, and hemorrhagic. It pushes on the adjacent vertebral body that shows thickened cortex ⇨, but no involvement of the bone was identified.*

### Chordoma of Vertebral Body



### Destructive Tumor of Distal Coccyx

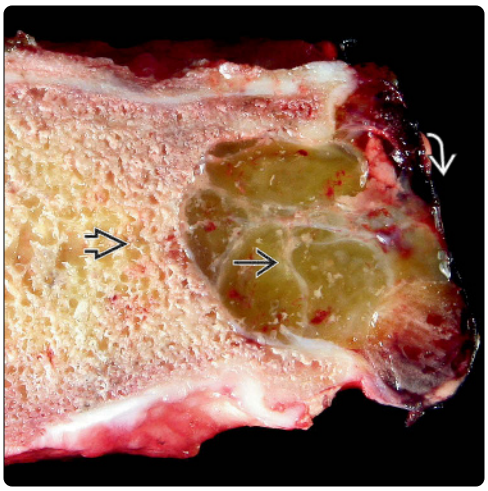


**(Left)** *Chordoma arising in the vertebral body with extraosseous extension is shown. The tumor in the vertebra is mixed sclerotic and gelatinous, whereas the extraosseous component is gelatinous and lobulated.* **(Right)** *A sagittal section through a large chordoma that developed in and destroyed the distal coccyx is shown. The residual vertebral bodies are permeated by tumor ⇨. The tumor is well circumscribed, has a nodular architecture, and is tan-gray, hemorrhagic, and focally myxoid.*

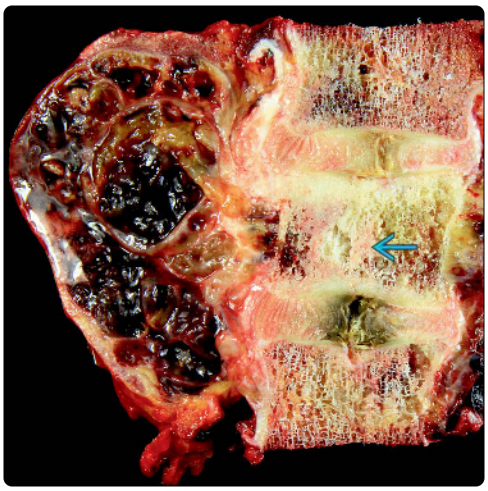


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### Spinal Canal Extension

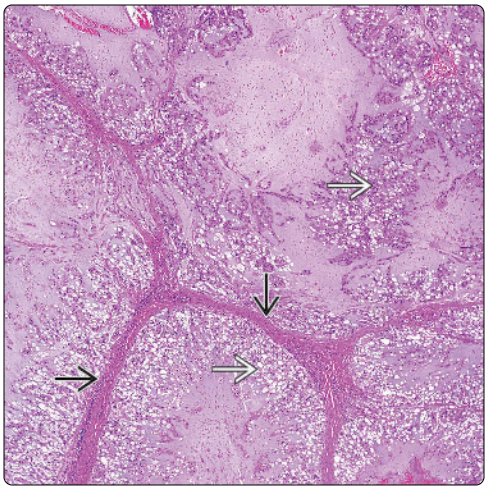


### Hemorrhagic Soft Tissue Extension

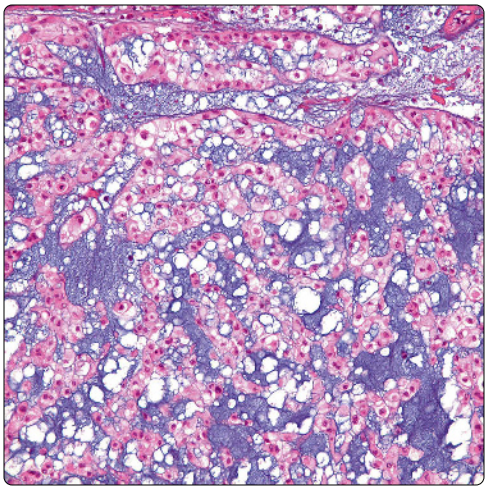


**(Left)** *A chordoma located posteriorly in a vertebral body bulges into the spinal canal. The circumscribed mass is tan-pale green. The anterior sclerotic bone contains a BNCT.* **(Right)** *This chordoma arises in the vertebral body where it is somewhat sclerotic but extends into the adjacent soft tissue where the tumor is extensively gelatinous and hemorrhagic.*

### Lobular Growth Pattern

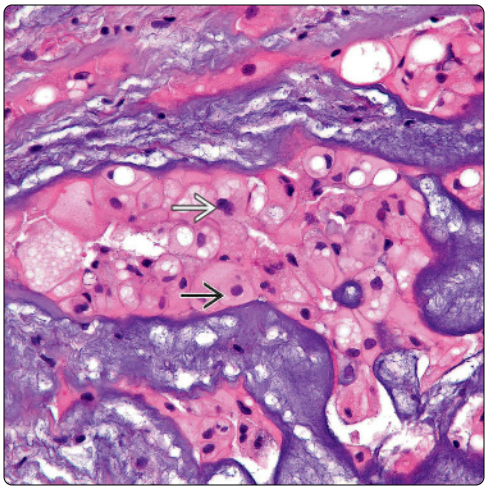


### Cohesive Cords of Cells

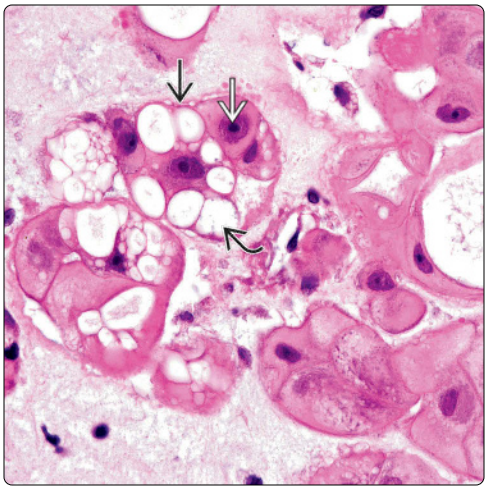


**(Left)** *This chordoma has a lobular growth pattern and is subcompartmentalized by fibrous septa. The stroma is usually prominent, basophilic, and myxoid in appearance and contains abundant glycosaminoglycans. The tumor cells are arranged in cords and aggregates variable in size.* **(Right)** *Chordoma cells grow in a spectrum of patterns. The most common are cords and cohesive aggregates of variable size. The cells seem to float in a basophilic mucinous stroma.*

### Cohesive Polyhedral Cells



### Physaliphorous Cells

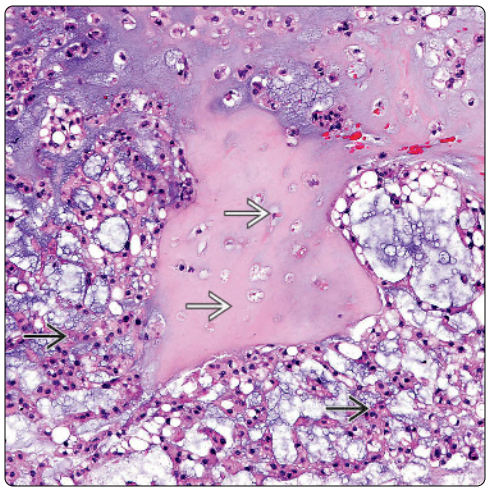


**(Left)** *Classic chordoma cells are large, polyhedral, contain abundant eosinophilic cytoplasm, and have oval to round nuclei with fine chromatin. The size, shape, and degree of hyperchromasia of nuclei are variable.* **(Right)** *Characteristic of chordoma is the physaliphorous cell present in most tumors. The cell contains intracytoplasmic, sharp, clear vacuoles, which cause it to have a bubbly appearance. The cell nuclei may contain prominent nucleoli.*

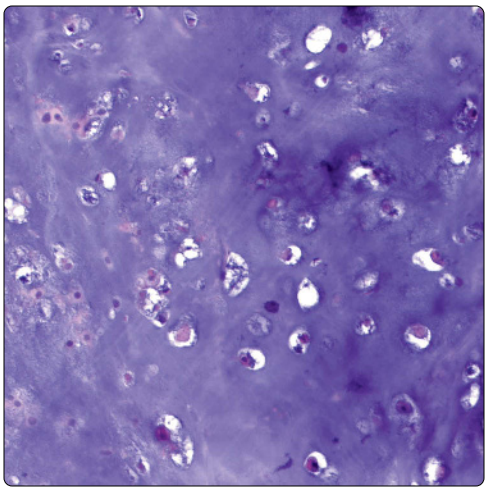


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### Hyaline-Type Cartilage

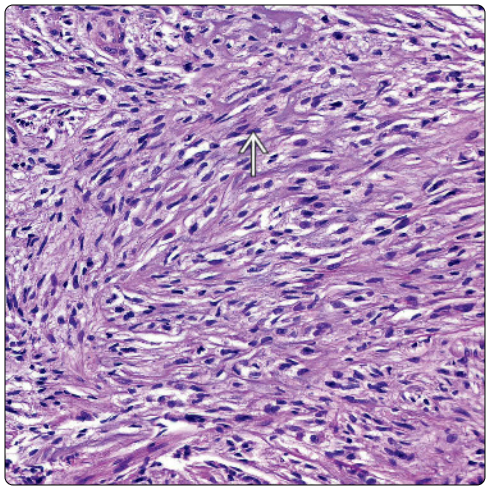


### Chondroid Chordoma

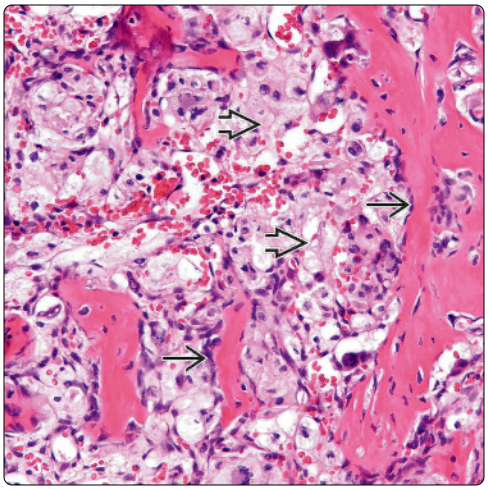


**(Left)** *Chondroid chordomas are most often seen in the skull base. The tumor is composed of conventional chordoma ⇨ with areas that closely resemble neoplastic hyaline cartilage ➡. In the chondroid regions, the cells are distributed singly and reside in lacunar spaces.* **(Right)** *This chondroid chordoma contained large areas of chondroid differentiation mimicking a cartilaginous tumor. The cells stained for keratin and brachyury, and in other areas, conventional chordoma was seen.*

### Spindle-Shaped Chordoma Cells

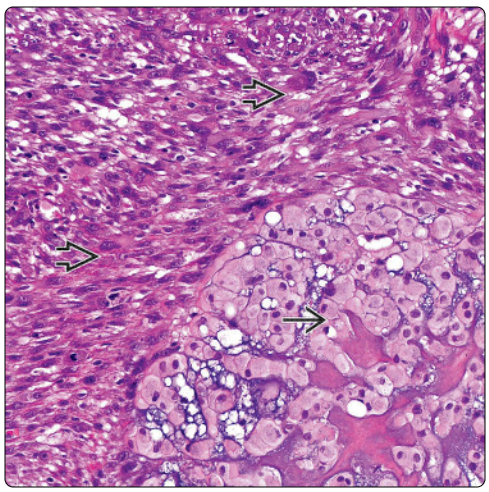


### Reactive Bone Formation

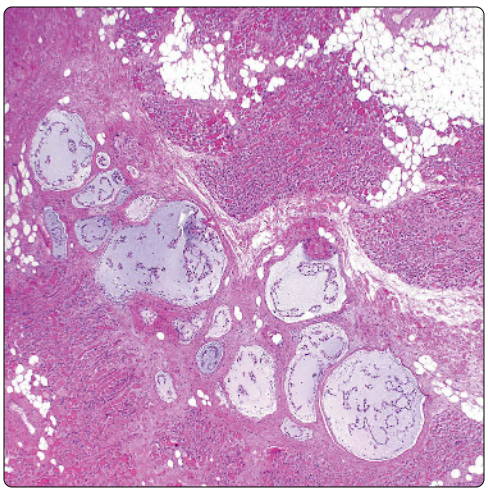


**(Left)** *Chordoma cells are sometimes elongate and spindle-shaped ➡ and arranged in swirling fascicles. The tumor cells have eosinophilic cytoplasm and cigar-shaped nuclei. Myxoid matrix and epithelioid cells are usually present.* **(Right)** *In a minority of cases, chordoma cells elicit a prominent bony reaction: Groups of tumor cells ⇨ are delineated by trabeculae of woven bone rimmed by prominent osteoblasts ⇨. This appearance can mimic clear cell chondrosarcoma.*

### Dedifferentiated Chordoma



### Soft Tissue Local Recurrence

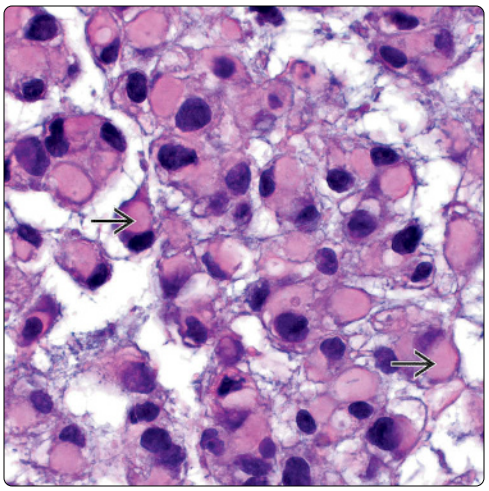


**(Left)** *A dedifferentiated chordoma contains areas of conventional chordoma ⇨ juxtaposed to areas that have the appearance of a pleomorphic spindle cell sarcoma ⇨.* **(Right)** *Typical appearance of soft tissue local recurrence in chordoma is shown. The recurrent tumor forms numerous nodular tumor deposits, many of which are microscopic in appearance.*

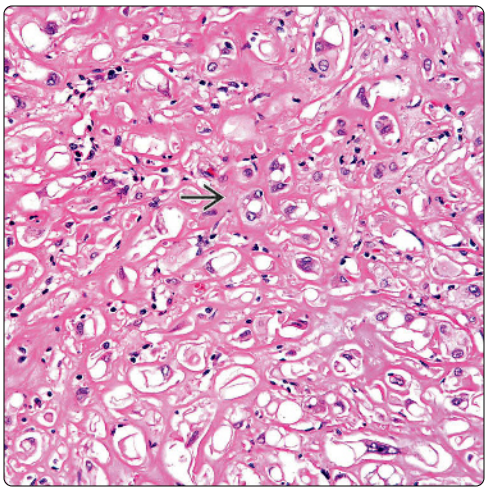


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### Rhabdoid Appearance

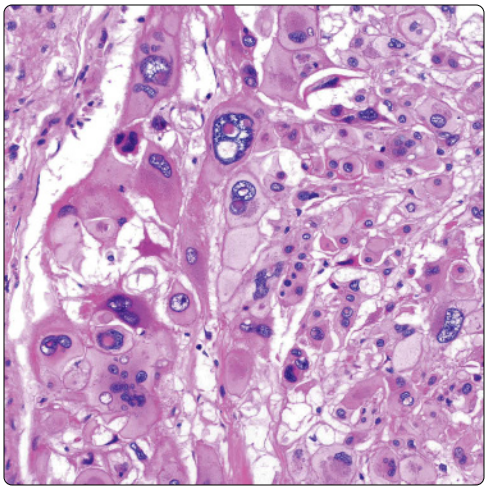


### Hyalinized Stroma

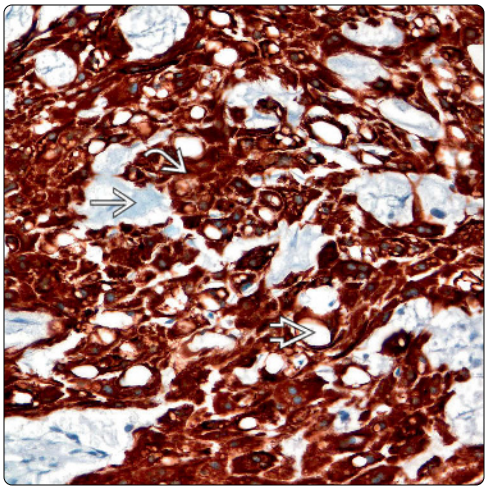


**(Left)** *Some conventional chordomas contain neoplastic cells that are rhabdoid in appearance. These cells have eccentric globular eosinophilic inclusions that displace the nuclei peripherally. The cells are surrounded by basophilic flocculent myxoid stroma.* **(Right)** *In a minority of chordomas, the stroma can become hyalinized, encasing tumor cells in eosinophilic matrix. The cells can be arranged in linear arrays, causing diagnostic confusion with epithelioid hemangioendothelioma.*

### Degenerative Atypia

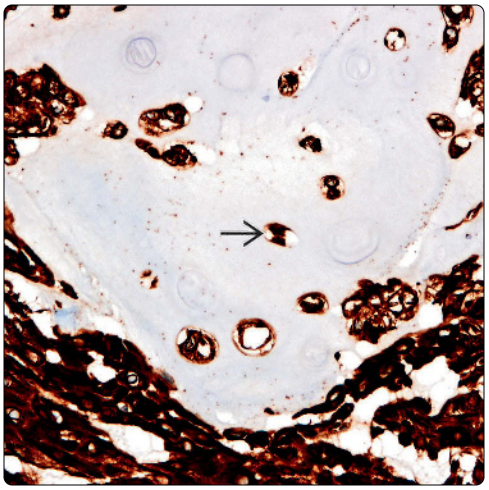


### Keratin Stain in Conventional Chordoma

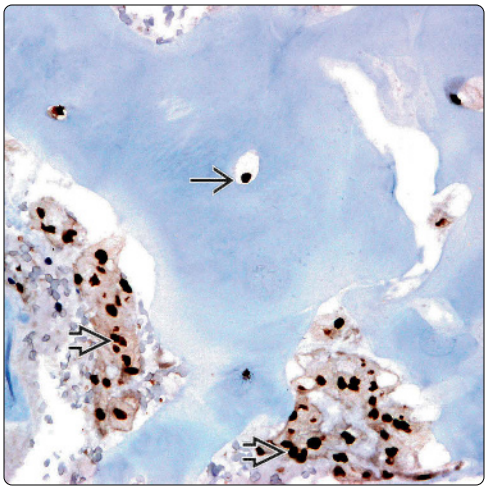


**(Left)** *Sometimes chordomas show degenerative atypia with enlarged hyperchromatic cells. Although worrisome histologically, these features have no clinical significance, and these tumors do not behave in a more aggressive fashion.* **(Right)** *Chordomas are strongly positive for keratin. Virtually all of the cells show prominent diffuse cytoplasmic expression of the antigen. The myxoid stroma and physaliphorous vacuoles stand out in contrast to the staining cytoplasm.*

### Keratin Stain in Chondroid Chordoma



### Brachyury Stain in Chondroid Chordoma

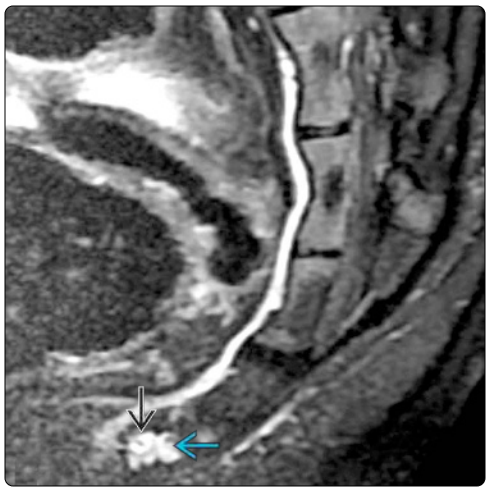


**(Left)** *Chondroid chordoma has areas of conventional chordoma and regions that closely mimic neoplastic hyaline cartilage. Keratin AE1/AE3 stains all the cells in the tumor, including those in the chondroid matrix. This reaction helps distinguish the tumor from chondrosarcoma, which is invariably negative.* **(Right)** *Chondroid chordoma also expresses brachyury. The positive nuclei are present in single cells surrounded by chondroid matrix and those that grow in groups.*

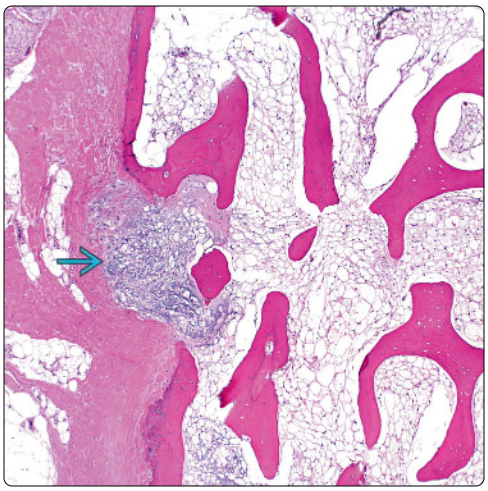


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### Small Chordoma Arising in BNCT



### Small Chordoma Arising in BNCT

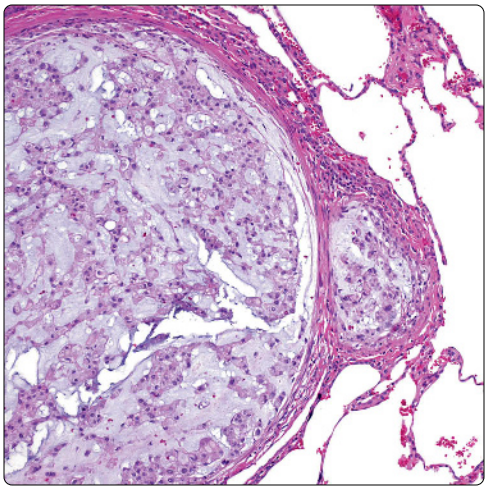


**(Left)** *Very small chordoma of the distal coccyx is shown. The intraosseous tumor ⇨ histologically represents a BNCT, whereas the small bright extraosseous component represents a small conventional chordoma ⇨.* **(Right)** *This is the corresponding resection specimen. The intraosseous portion of the tumor has the classic features of a BNCT. A small conventional chordoma is present that has broken through the bone with extension into the adjacent soft tissue ⇨.*

### Metastatic Chordoma to Lungs

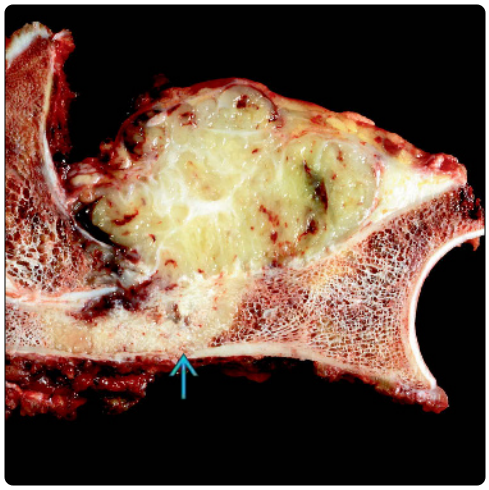


### Metastatic Chordoma to Lungs

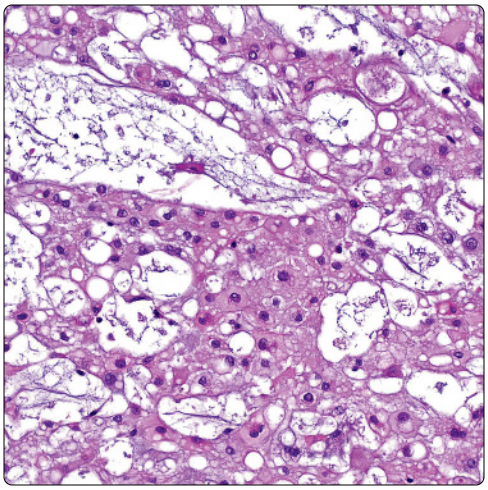


**(Left)** *Lung is one of the more common sites for metastatic disease. This axial CT scan shows a nodule of metastatic conventional chordoma ⇨.* **(Right)** *This wedge resection of metastatic chordoma to the lungs shows 2 small deposits of conventional chordoma.*

### Extraaxial Chordoma of Pelvis



### Extraaxial Chordoma

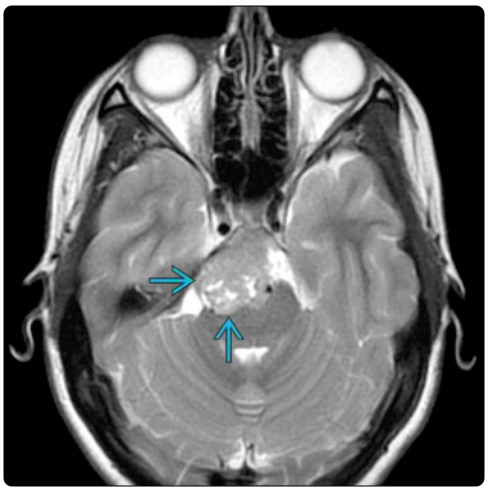


**(Left)** *Chordoma of the pelvis with no involvement of the adjacent sacrum is shown. The tumor arises in the bone ⇨ and forms a large intrapelvic gelatinous mass.* **(Right)** *The corresponding histology of the resection specimen of the pelvic chordoma shows the characteristic features of a conventional chordoma, the tumor being composed of cohesive cells with eosinophilic cytoplasm embedded in an extracellular myxoid matrix.*

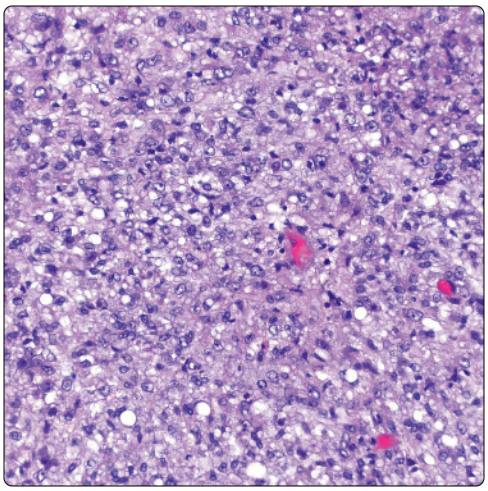


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Poorly Differentiated Chordoma

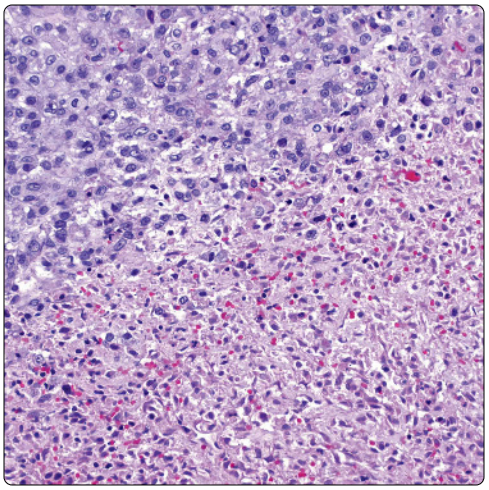


Poorly Differentiated Chordoma

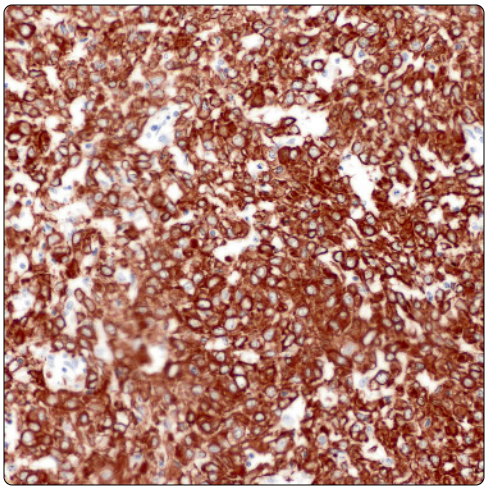


**(Left)** *A poorly differentiated chordoma arising in the skull base of a young individual is shown. The tumor is large, destructive, and pushes on adjacent structures.* **(Right)** *Typical poorly differentiated chordoma is shown. The tumor is cellular, being composed of atypical cells with large nuclei, some with large eosinophilic nucleoli. There is no extracellular myxoid matrix as classically seen in conventional chordoma.*

Areas of Necrosis

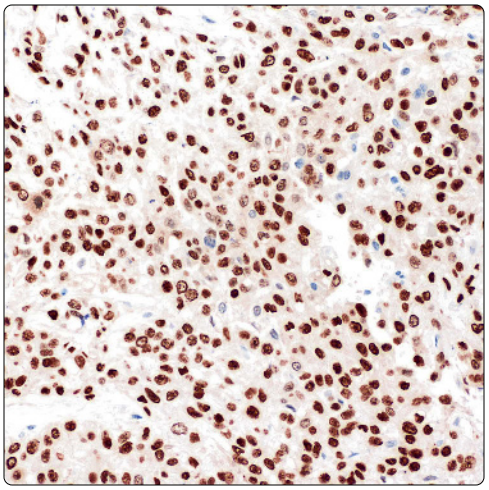


Keratin Immunohistochemical Stain

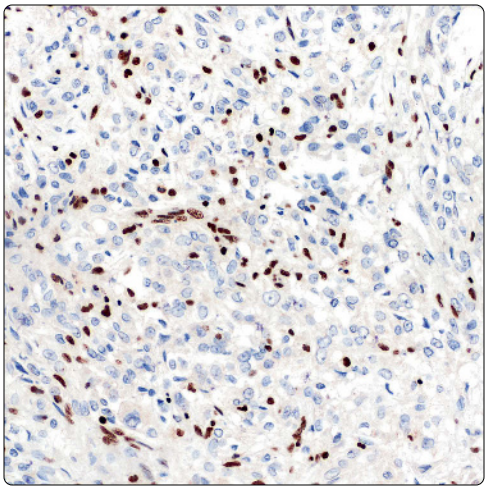


**(Left)** *Areas of necrosis are a common finding in poorly differentiated chordomas.* **(Right)** *Diffuse keratin stain in a poorly differentiated chordoma is shown. The poorly differentiated chordomas have the same immunohistochemical profile as conventional chordoma. Sometimes, these tumors are misdiagnosed as metastatic carcinoma.*

Brachyury Immunohistochemical Stain



INI1 Immunohistochemical Stain



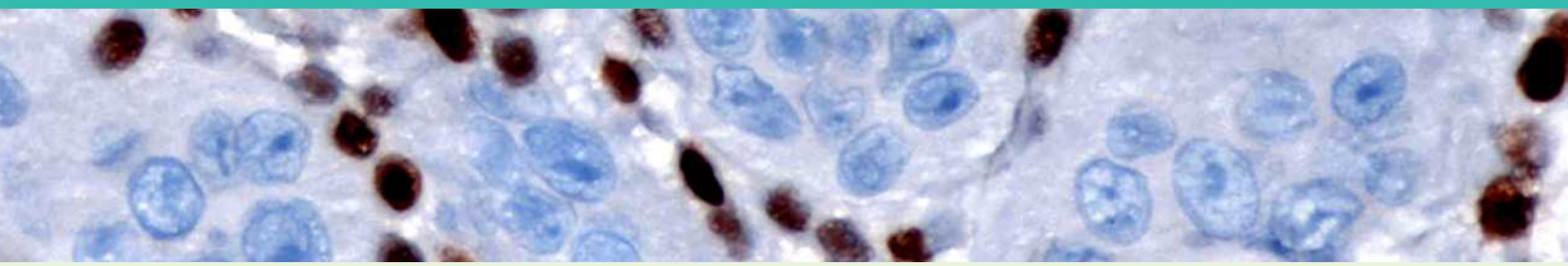
**(Left)** *Diffuse brachyury stain in a poorly differentiated chordoma is shown. The poorly differentiated chordomas show nuclear staining for brachyury as conventional chordoma.* **(Right)** *Poorly differentiated chordoma shows loss of staining for INI1. This is typically seen in poorly differentiated chordomas and can cause confusion with atypical teratoid rhabdoid tumor, which also slows loss of INI1. Normal endothelial cells and inflammatory cells retain INI1 staining.*

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SECTION 9

# Giant Cell–Rich Tumors




| | |
|---|---|
| Giant Cell Tumor | **256** |
| Brown Tumor | **270** |
| Giant Cell Reparative Granuloma | **274** |


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KEY FACTS

## TERMINOLOGY

- Neoplasm composed of cytologically benign, oval or polyhedral mononuclear cells that are admixed with numerous, evenly distributed, osteoclast-like giant cells

## ETIOLOGY/PATHOGENESIS

- Driver mutation in *H3F3A* histone gene

## CLINICAL ISSUES

- Represents ~ 5% of primary bone tumors
- Most arise in epiphyseal-metaphyseal region of long tubular bones
- Pain and swelling
- Treated by curettage; local recurrence 25%
- 1-2% of giant cell tumors (GCTs) eventually metastasize, primarily to lungs
- Receptor activator of NF-κB (RANK) ligand inhibitor denosumab effective and may supplement radiation treatment and surgery in difficult cases

## IMAGING

- Large, lytic, cystic degeneration

## MACROSCOPIC

- Friable, hemorrhagic, red-brown

## MICROSCOPIC

- Mononuclear cells are diagnostic and neoplastic component of tumor
- Numerous, multinucleated osteoclast-like giant cells that are scattered evenly throughout tumor

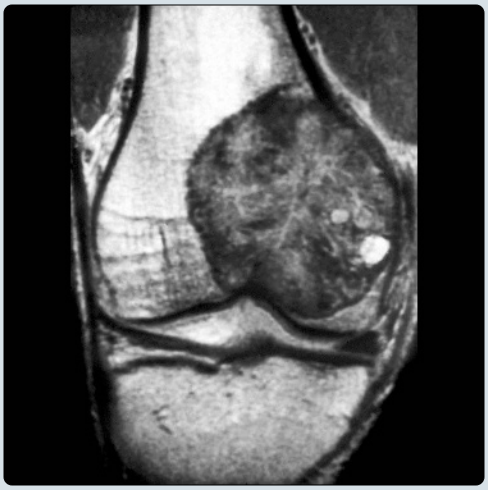
## TOP DIFFERENTIAL DIAGNOSES

- Nonossifying fibroma/benign fibrous histiocytoma
- Chondroblastoma
- Giant cell reparative granuloma/brown tumor
- Aneurysmal bone cyst
- Giant cell-rich osteosarcoma

**Large Lytic Tumor**

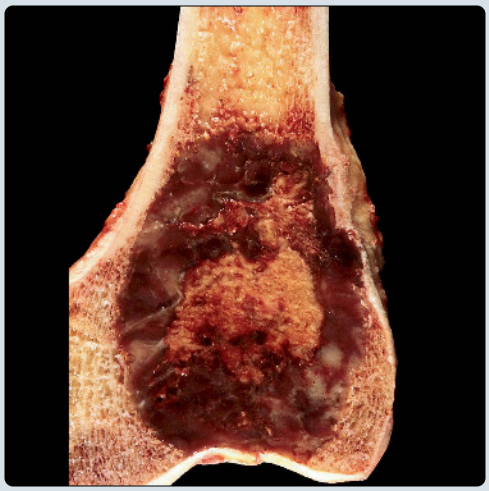


**Tumor Extends to Base of Articular Surface**

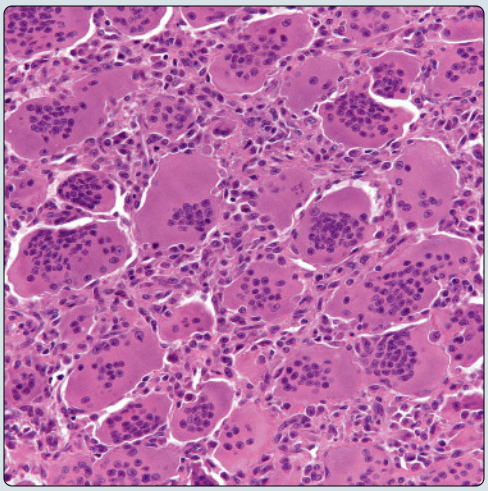


**(Left)** *A giant cell tumor (GCT) of bone involving the distal femur demonstrates a lytic, subarticular, and geographic lesion. There is neither reactive sclerosis nor internal matrix. The medial condyle is slightly expanded with the cortex being blurred.* **(Right)** *Coronal T2-weighted MR shows a GCT involving the distal femur. The tumor is well-defined and heterogeneous with a dark rim extending to the subchondral plate. The adjacent marrow is normal.*

**Hemorrhagic, Tan Mass**



**Numerous Giant Cells**



**(Left)** *GCT of bone arising in the distal femur is predominantly red-brown-tan, involves the metaphysis and distal diaphysis, and extends into the epiphysis to the subchondral plate.* **(Right)** *Syncytial growth of mononuclear cells are admixed with numerous osteoclast-like giant cells. The nuclei of the mononuclear cells are morphologically identical to those in the giant cells, which is diagnostic of GCT of bone.*



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## TERMINOLOGY

### Abbreviations

- Giant cell tumor (GCT)

### Synonyms

- Osteoclastoma

### Definitions

- Benign locally aggressive neoplasm composed of cytologically banal, oval or polyhedral mononuclear cells admixed with numerous, evenly distributed, osteoclast-like giant cells

## ETIOLOGY/PATHOGENESIS

### Neoplastic

- Mononuclear cells are neoplastic with possible osteoblast phenotype that induce formation of osteoclast-type giant cells by expressing receptor activator of NF-κB (RANK) ligand
  - Osteoclast-type giant cells express receptor RANK that binds to RANK ligand on mononuclear cells
- Driver mutation in *H3F3A* histone gene

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Represents 5% of primary bone tumors; 1.2 per million per year
    - Accounts for 20% of benign bone tumors
- Age
  - Develops in skeletally mature individuals during 3rd-5th decades; mean age: 34 years
  - Rarely occurs in children
- Sex
  - Females are affected slightly more frequently than males

### Site

- Vast majority arise in epiphyseal-metaphyseal region of long tubular bones
- When growth plates open, tumors may be centered in metaphysis and abut epiphyseal plate
  - Rarely arise in diaphysis
- In almost 1/2 of cases, GCT develops around knee; distal femur followed by proximal tibia and distal radius
- Uncommon sites are vertebral bodies, bones of hands and feet, craniofacial bones, and patella
  - Some GCTs in craniofacial skeleton occur in setting of Paget disease of bone
- Usually solitary
  - 1% of cases are multifocal, and these often affect bones of hands and feet

### Presentation

- Pain, swelling, pathologic fracture in minority of cases

### Treatment

- Surgical approaches
  - Usually treated by thorough curettage with adjuvant
  - En bloc resection for large tumors with little residual structural bone
- Drugs
  - RANK ligand inhibitor denosumab effective and may supplement radiation treatment and surgery in difficult cases
    - Tumor locally recurs if drug therapy is discontinued
- Radiation
  - Used in surgically inaccessible tumors, when surgical treatment would result in significant morbidity, or when medical problems preclude surgical intervention

### Prognosis

- Local recurrence rate ~ 25% for patients treated with curettage, usually within 3 years
- Although GCT of bone is classified as benign neoplasm, it is well recognized that 1-2% eventually metastasize, primarily to lungs
  - Metastatic deposits frequently cured by resection
  - Metastatic disease can also be treated with RANK ligand inhibitors, such as denosumab
  - Metastases occur more frequently in patients with pathologic fracture or following multiple curettages for recurrent disease
- Uncommon complication is development of sarcoma within GCT (8%)
  - This may occur de novo, develop in locally recurrent tumor, or happen following radiation therapy

## IMAGING

### Radiographic Findings

- Large, lytic, intramedullary and frequently eccentric
- Usually extends from metaphysis to subchondral bone plate
  - Very large tumors may involve adjacent diaphysis, focally destroy cortex, and invade into neighboring soft tissues
- May expand bone and elevate periosteum
  - Results in thin periosteal shell of reactive bone, which may be incomplete
- Medullary margins are well defined, may have moth-eaten appearance, and are usually not sclerotic
- Cystic degeneration is common secondary finding (aneurysmal bone cyst-like changes)
- After RANKL inhibitor therapy, tumor shows increased sclerosis/bone formation

### MR Findings

- Low to intermediate signal on T1- and T2-weighted images
- T1 is better to see intramedullary component of tumor
- T2 is better to evaluate extraosseous component of large tumors and to identify any cystic changes (fluid-fluid levels)

### CT Findings

- Tumor is lytic with well-defined borders

### Bone Scan

- Increased uptake on technetium scan

## MACROSCOPIC

### General Features

- Friable, hemorrhagic, red-brown



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- Solid or focally cystic
- Erodes cortex
- Well-delineated margins within medullary canal and in neighboring soft tissues

### Sections to Be Submitted

- 10 cassettes for curettage specimens
- Resection specimens: Bone and soft tissue margins, minimum of 1 section per cm of tumor

### Size

- Typically range from 5-15 cm in dimension

## MICROSCOPIC

### Histologic Features

- Mononuclear stromal cells are diagnostic and neoplastic component of tumor
- Numerous multinucleated osteoclast-like giant cells are scattered evenly throughout tumor
  - Number of nuclei in any individual cell variable but may be as many as 50 or more
- Mononuclear cells appear to grow in syncytium, have ill-defined cell borders, and little eosinophilic cytoplasm
- Tumor cell nuclei are round or ovoid, vesicular, have central nucleoli, and are morphologically identical to nuclei of giant cells
- Mononuclear cells may be mitotically active and can show variable degrees of cytologic atypia
  - Atypia may be prominent in areas admixed with previous hemorrhage and fibrin deposition
- Foci of necrosis and vascular invasion may be present
- Tumor can demonstrate benign fibrous histiocytoma (BFH)-like areas that are devoid of classic mononuclear and osteoclast-type giant cells
- Other secondary changes commonly encountered in GCT include hemosiderin deposits, aggregates of foamy macrophages, cystic changes, and reactive bone formation
- Following RANKL inhibitor therapy, giant cells disappear, mononuclear tumor cells decrease, and bone formation increases
- Soft tissue recurrence is frequently surrounded by shell of reactive bone

### Ultrastructural Features

- Abundant dilated rough endoplasmic reticulum, well-developed Golgi apparatus, mitochondria, and occasional lipid droplets
  - None of these features are specific for GCT of bone

## ANCILLARY TESTS

### Immunohistochemistry

- Giant cells have immunoprofile similar to macrophages
- Osteoclast-type giant cells stain for RANK
- Many of stromal mononuclear tumor cells stain for RANKL, indicating that they may have osteoblastic phenotype
- Mononuclear tumor cells show nuclear staining for p63

## DIFFERENTIAL DIAGNOSIS

### Nonossifying Fibroma/Benign Fibrous Histiocytoma

- Most GCTs have areas that resemble nonossifying fibroma (NOF) or BFH
  - Areas are composed of banal spindle cells arranged in storiform pattern with scattered osteoclast-like giant cells
- Spindle cell component is frequently located at periphery of tumor and is not diagnostic of GCT
- True NOF/BFH does not have foci characteristic of GCT

### Chondroblastoma

- Seen in skeletally immature individuals with open growth plate and is centered in epiphysis
- Mononuclear cells do not resemble nuclei of osteoclast-type giant cells as seen in GCT of bone
- "Chicken-wire" calcifications and chondroid areas of chondroblastoma not present in GCT of bone
- Tumor cells stain for S100 but usually negative for p63

### Giant Cell Reparative Granuloma/Brown Tumor

- Osteoclast-type giant cells cluster in areas of hemorrhage
  - GCT of bone: Giant cells evenly distributed
- Cells are spindle-shaped: Do not resemble nuclei in osteoclast-type giant cells

### Aneurysmal Bone Cyst

- Difficult to distinguish between primary aneurysmal bone cyst and cystic GCT of bone
- Cystic GCT of bone: Characteristic morphology must be present
- Has t(16;17) identifiable by FISH

### Giant Cell-Rich Osteosarcoma

- Tumor grows with infiltrative pattern
- Contains cytologically malignant mononuclear cells

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Lytic lesion in distal long bone extending to subchondral area in adult is characteristic

### Pathologic Interpretation Pearls

- Proliferation of mononuclear cells and evenly distributed osteoclast-type giant cells
  - Nuclei of mononuclear cells identical to those of osteoclast-type giant cells
- If needle biopsy looks like fibrous histiocytoma, think possible GCT

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2. Wojcik J et al: Denosumab-treated giant cell tumor of bone exhibits morphologic overlap with malignant giant cell tumor of bone. Am J Surg Pathol. 40(1):72-80, 2016
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**Moth-Eaten Margins**



**Elongate Intramedullary Tumor**



**(Left)** *Radiograph of a GCT arising in the distal femur shows a vague geographic lytic lesion. The proximal margin has a moth-eaten appearance and is ill defined. The distal medial margin has a sclerotic rim. There is endosteal thinning of the distal lateral cortex.* **(Right)** *T1-weighted coronal MR of a GCT clearly shows the long extent of the lesion. The tumor is heterogeneous in signal intensity with a thin, dark rim. The tumor extends deep in the intercondylar notch. The adjacent marrow is normal.*

**Lytic Tumor With Moth-Eaten Margin**



**Large Mass With Extension Into Soft Tissue**

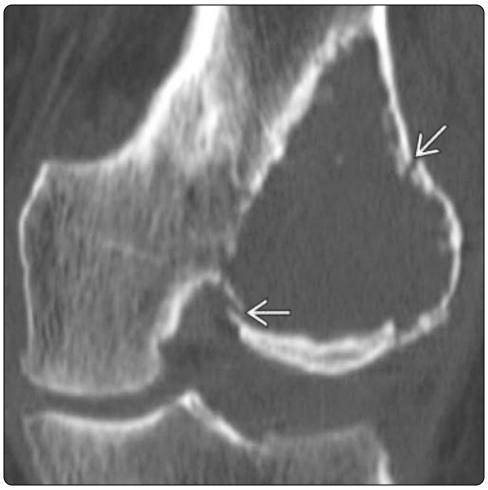


**(Left)** *Radiograph of a GCT of the distal femur shows a lytic lesion with thinning and penetration of the anterior cortex. The distal margin has a thin, sclerotic rim, and the proximal margin is moth-eaten. No soft tissue extension is present.* **(Right)** *Sagittal T2-weighted MR of a GCT of the distal femur shows a well-defined heterogeneous lesion with cortical penetration anteriorly and a small soft tissue component. Note the focal cortical thinning posteriorly.*

**Radiolucent Tumor With Sclerotic Margin**



**Lytic Tumor With Pathological Fracture**



**(Left)** *A lytic GCT occupies the distal lateral femur and has irregular, geographic, and sclerotic margins. The lateral cortex is penetrated, and there is a pathologic fracture with surrounding periosteal new bone formation.* **(Right)** *Coronal CT scan shows a GCT of the distal femur that is lytic, uniformly hypodense, and subarticular with sclerotic margins. There is a fracture through the lateral cortex and condyle with intraarticular extension.*

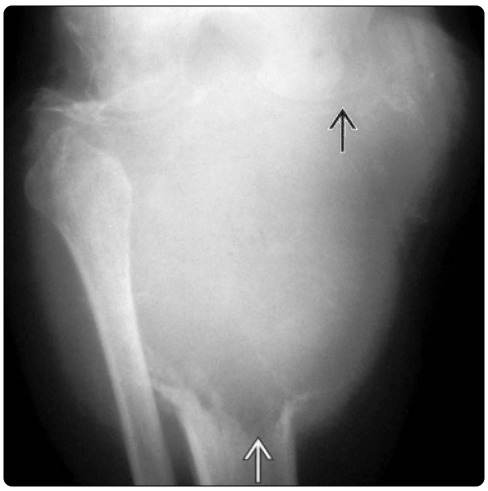


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**Palpable Multinodular Tumor**



**Destructive Tumor**

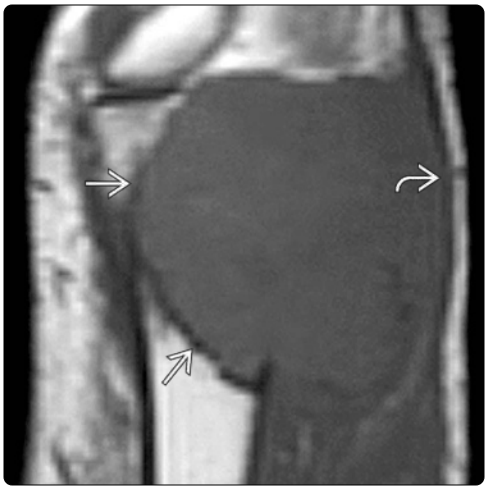


**(Left)** *This patient has a GCT of the proximal tibia that presented as a painful mass. The tumor is multinodular and bulges the overlying skin in multiple areas. In areas, the attenuated skin is erythematous.* **(Right)** *Radiograph of a GCT of the proximal subarticular tibia shows a "blow-out" lesion with expanded medial and lateral cortices and a geographic distal margin. The lytic tumor extends up to the base of the subchondral bone plate.*

**Lytic Tumor With Focally Sclerotic Margins**

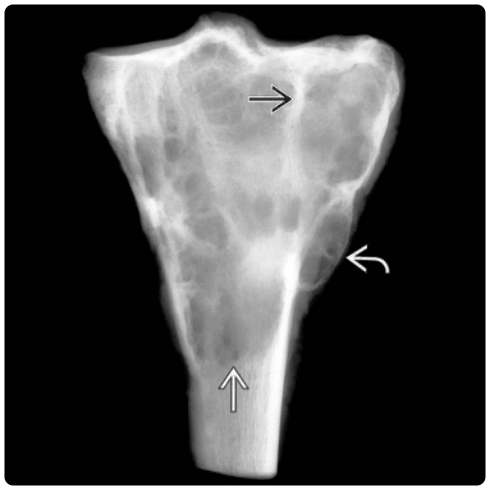


**Prominent Extension Into Soft Tissue**



**(Left)** *Radiograph shows a GCT involving the proximal subarticular lateral tibia. The tumor is radiolucent and destroys the lateral cortex, but the medial margin is better defined and focally sclerotic.* **(Right)** *Coronal T1-weighted MR of a GCT shows expansion of the lateral portion of the tibia; the tumor is confined by a thin shell of periosteal new bone. The medial margin shows the dark rim characteristic of GCT.*

**Resected Tumor**



**Tan, Expansile Mass**



**(Left)** *Specimen radiograph of a GCT involving the proximal tibia shows a multiloculated, subarticular lytic lesion with focal areas of cortical expansion, internal septation, and a well-demarcated distal margin.* **(Right)** *Accompanying gross photograph of the previous specimen radiograph shows a GCT arising in the proximal tibia. The tumor is tan-yellow and extends to the base of the articular cartilage and has broken through the cortex laterally where it is surrounded by a thin layer of periosteal new bone.*



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### Lytic Tumor With Poorly Defined Margins



### Pathological Fracture

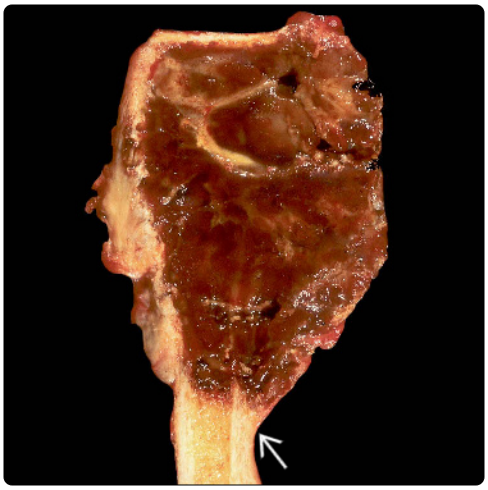


**(Left)** *GCT of the proximal lateral tibia is lytic and has poorly defined proximal margins. The tumor extends into the medial portion of the bone.* **(Right)** *The same tumor in the same patient after the passage of 3 months is shown. The tumor has enlarged and produced a greater amount of bone destruction. As a result, a displaced pathological fracture has developed.*

### Large Moth-Eaten Mass



### Expansile, Red-Brown Mass

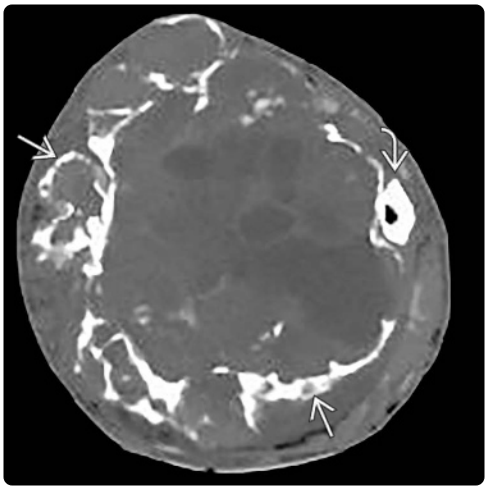


**(Left)** *Radiograph of a GCT in the distal radius has a blow-out appearance with destruction of the lateral cortex and soft tissue extension. The medial and proximal margins are moth-eaten, and the tumor extends to the subchondral bone plate.* **(Right)** *GCT arising in the distal radius is solid, dark brown, and involves the metaphysis, diaphysis, and epiphysis. The tumor extends to the subchondral bone plate and has broken through the cortex, forming a soft tissue mass. Note the periosteal new bone proximally.*

### Huge Tumor of Radius



### Huge Expansile Destructive Tumor

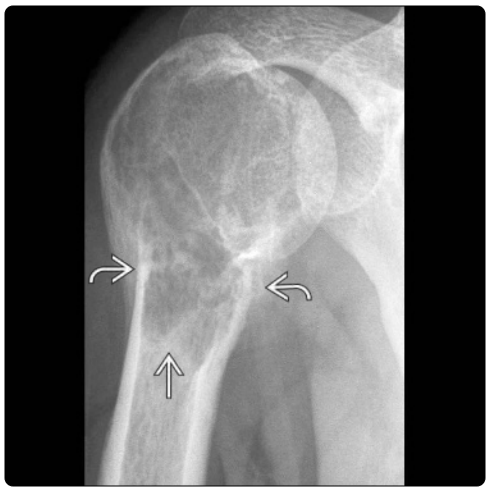


**(Left)** *This patient has an enormous GCT of the distal radius. The tumor forms a large palpable mass with engorgement of blood vessels in the skin overlying the tumor.* **(Right)** *This is the CT of the previous clinical photograph. The tumor has destroyed the radius and is confined by a peripheral rim of reactive bone. The ulna is uninvolved by the adjacent mass.*

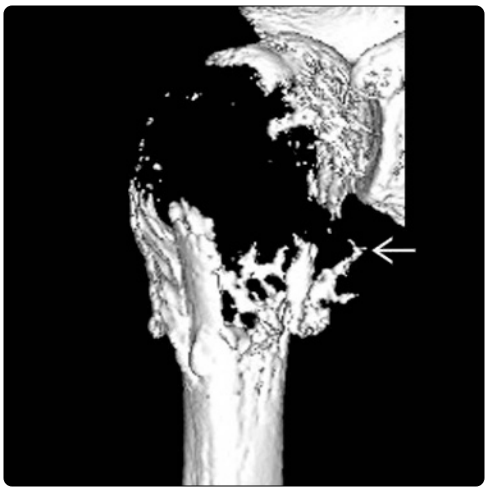


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### Pathological Fracture



### Destructive Mass With Fracture

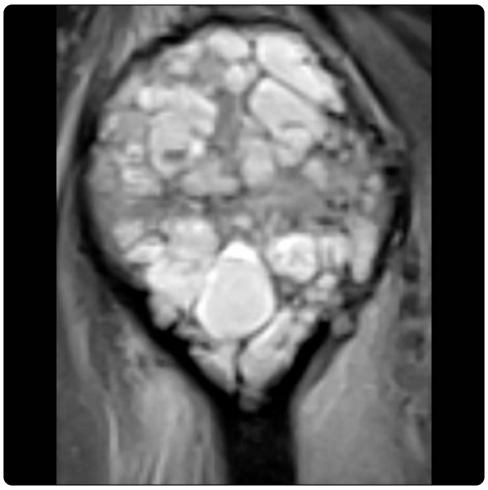


**(Left)** *A geographic lytic lesion in the subarticular humerus has caused a previous fracture, which is healing with callus. Thick periosteal new bone is seen at the fracture site both medially and laterally. The distal margin is relatively well defined.* **(Right)** *3D reconstructed CT scan shows the lytic, expanded GCT in the proximal humerus that has produced a pathologic fracture. There is periosteal new bone along the medial and lateral cortex at the fracture site.*

### Expansile, Lytic Mass



### Multiple Cysts



**(Left)** *The proximal fibula is massively expanded by a lytic tumor that has internal trabeculations. The periphery of the tumor is delineated by subperiosteal newly formed bone, and the distal margin has a short zone of transition.* **(Right)** *The accompanying coronal proton density MR shows that the GCT in the fibula contains many large cysts, and some of the cysts have fluid-fluid levels. GCT is known to undergo secondary aneurysmal bone cyst-like change.*

### Large Mass Extending Into Thoracic Cavity



### Large Mass With Soft Tissue Extension

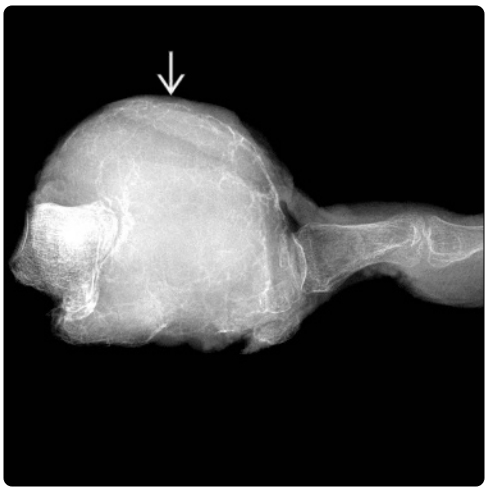


**(Left)** *Axial CT scan of a large GCT of bone shows a lytic lesion in the vertebral body extending into the right pedicle with a prominent heterogeneous subpleural component surrounded by a periosteal shell.* **(Right)** *Sagittal reformatted CT of a GCT shows a large subpleural mass with a periosteal shell and scattered internal densities. The mass extends into the adjacent transverse process with a small soft tissue component inferiorly.*

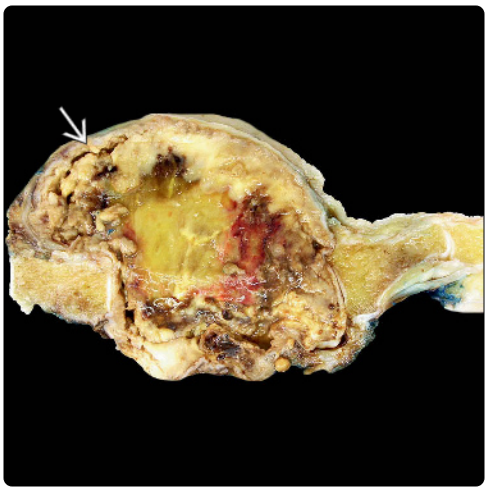


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### Large, Destructive Tumor



### Tan-Brown-Yellow Mass Destroying Bone

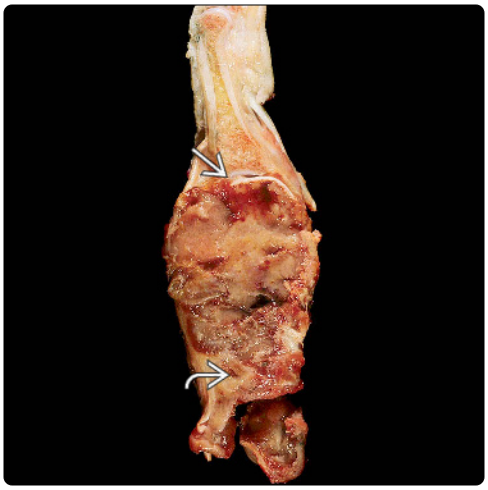


**(Left)** *Specimen radiograph of a GCT of bone arising in a metatarsal demonstrates a markedly expanded "blow-out" lesion involving the entire metatarsal. The tumor has destroyed the bone and is surrounded by a thin rim of reactive bone ➡. (Right) Gross photograph of a GCT of bone arising in a metatarsal demonstrates a large, tan-yellow tumor that has replaced the entire metatarsal. The tumor has destroyed the bone and has a large soft tissue component ➡.*

### Tumor Filling Metacarpal



### Predominately Solid Mass



**(Left)** *MR of a GCT of bone shows a homogeneously hypointense lesion involving the 5th metacarpal and expanding the distal dorsal aspect of the bone ➡ and bulging into the soft tissues. (Right) Photograph of a GCT involving the 5th metacarpal shows a tan, red-brown tumor that has replaced most of the bone, broken through the cortex, and extended into soft tissues. Distally, the tumor extends to the base of the preserved articular surface and involves the joint space ➡. Proximally, it is well demarcated ➰.*

### Lytic Tumor With Trabeculations



### Expansile Mass



**(Left)** *Radiograph of a GCT of the 1st metacarpal demonstrates a large "blow-out" lesion involving the entire bone. The lesion markedly expands the bone and is surrounded by an attenuated periosteal shell of reactive bone ➡. The lytic tumor has linear internal trabeculations. (Right) Axial CT of a GCT arising in the 1st metacarpal shows a large tumor that has expanded the bone and is surrounded by a thin rim of reactive periosteal new bone formation ➡. The tumor is homogeneous without an internal matrix.*

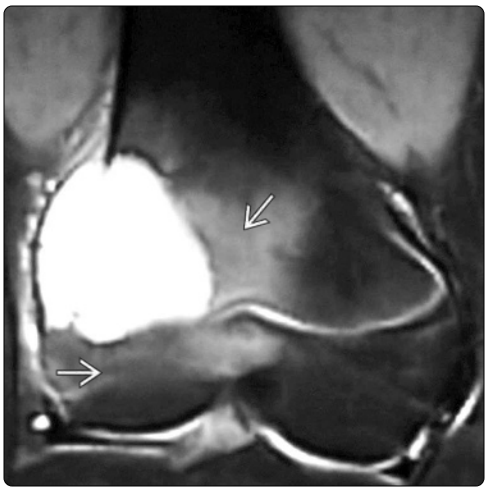


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### Metaphyseal Tumor in Adolescent

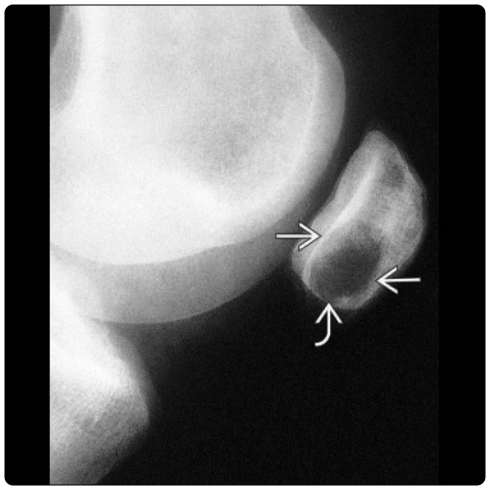


### Giant Cell Tumor in Young Patient

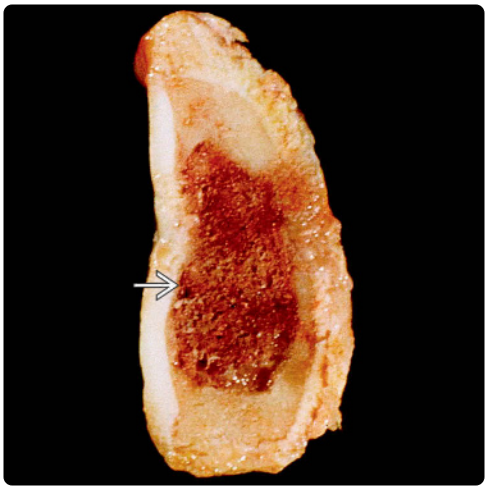


**(Left)** *Coronal CT reformat of a GCT in an adolescent with open growth plate involving the distal femoral metaphysis is shown. The tumor is lytic, erodes the cortex where it is confined by a thin periosteal shell, and minimally extends into the epiphysis. The medial portion of the tumor is well demarcated.* **(Right)** *Coronal fluid-sensitive MR of a GCT shows a hyperintense signal intensity lesion in the distal femoral metaphysis adjacent to the growth plate. The subtle bright signal in the adjacent marrow represents edema.*

### Oval, Radiolucent Tumor

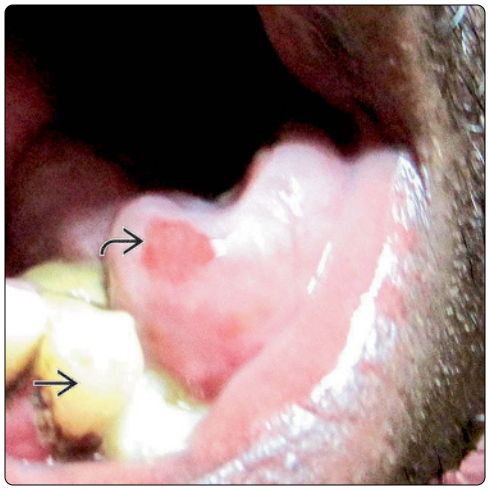


### Red-Brown-Tan Mass in Patella

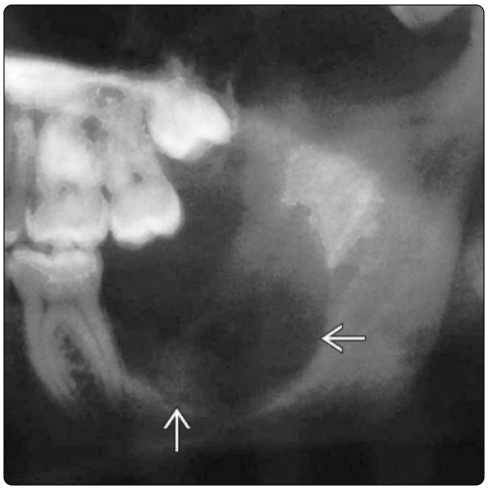


**(Left)** *Radiograph shows a GCT of bone arising in the patella. The tumor involves the inferior pole of the patella, is well defined and lytic with slightly sclerotic margins, and extends to the subchondral bone plate. Inferiorly, the homogeneous tumor erodes and thins the cortex.* **(Right)** *Gross photograph of a GCT arising in the patella shows that the tumor is well demarcated, solid, and red-brown-tan, and it extends to the subchondral bone plate. The articular surface is intact.*

### Ulcerated Tumor



### Round Lytic Tumor



**(Left)** *Clinical photograph shows a GCT arising in the mandible. The tumor has expanded the gingiva, displacing the teeth, and has caused ulceration of the mucosal lining.* **(Right)** *Radiograph of a GCT demonstrates an expansile geographic lesion in the mandible that erodes the inferior cortex. The tumor is homogeneously lytic, displaces the surrounding teeth, and shows no internal matrix. The margins of the mass are well defined.*

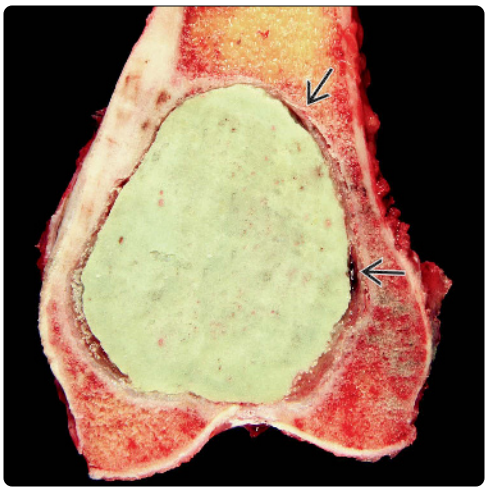


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### Recurrent Tumor



### Local Recurrence

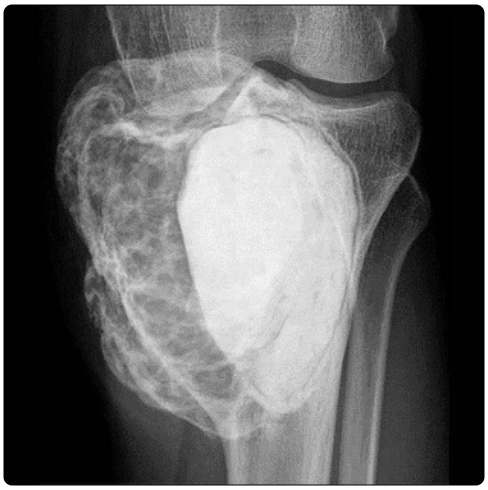


**(Left)** *Radiograph of a recurrent GCT shows a lobulated lytic lesion in the distal femur that surrounds bone cement packing and an intramedullary rod. The tumor scallops and thins the residual cortex and does not appear to extend into the soft tissues.* **(Right)** *Gross photograph shows a recurrent GCT involving the distal femur that had been previously packed with a solid plug of bone cement. The semilunar dark red tissue around the cement represents the recurrent tumor.*

### Large Recurrent Tumor

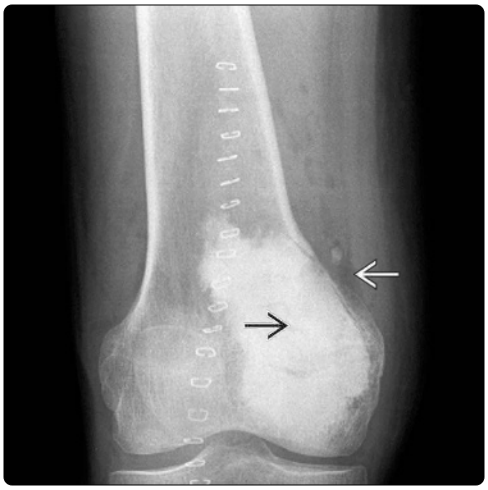


### Treatment Effect



**(Left)** *The GCT was previously curetted and packed with bone cement. The local recurrence is large, lytic, and expands the overlying cortex, which is composed of newly formed subperiosteal bone.* **(Right)** *This is the accompanying radiograph to the recurrent tumor in the previous image; the patient has been treated with denosumab for 8 months. There has been interval marked ossification of the tumor, which is now well demarcated. A needle biopsy showed no viable tumor.*

### Sarcomatous Transformation



### Malignant Degeneration

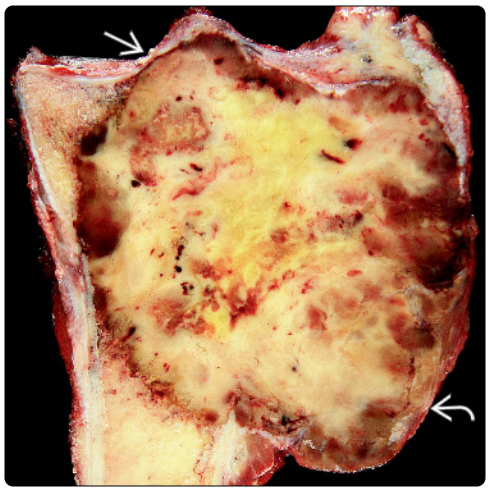


**(Left)** *Distal femur shows a sarcoma that has developed in a site previously treated with bone cement for conventional GCT of bone. The sarcoma produces a lucent area in the soft tissues.* **(Right)** *T2-weighted coronal MR shows sarcoma arising in a site previously treated for a GCT with curettage and bone cement packing (low-signal area). The sarcoma manifests as a large mass with heterogeneous high signal intensity in the femur and medial soft tissues.*

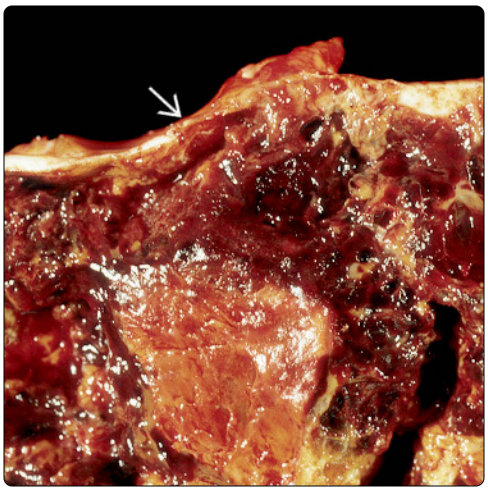


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**Large Solid Mass**

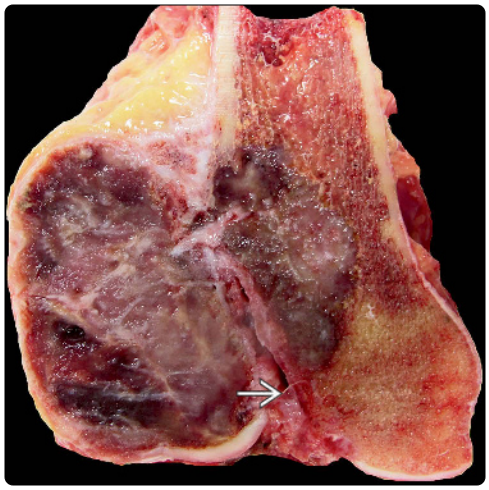


**Hemorrhagic Mass**

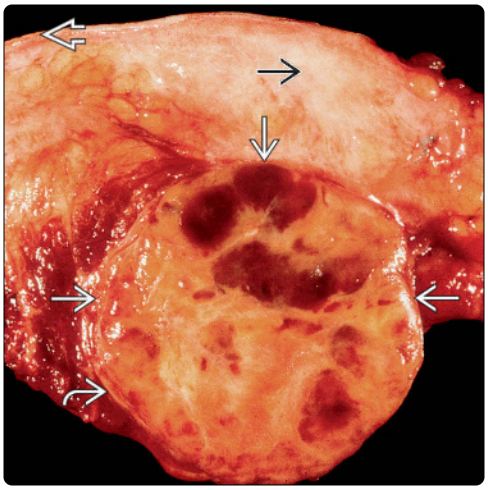


**(Left)** *GCT arising in the proximal tibia eccentrically involves the metaphysis and epiphysis and extends to the base of the articular surface. It has broken through the cortex and extends into soft tissue where it is covered by a rim of periosteal bone. The tumor is tan, yellow, and red-brown.* **(Right)** *A GCT of the proximal tibia extends into the subchondral bone plate. The hemorrhagic, red-brown and focally yellow tumor is friable and predominately solid.*

**Transarticular Fracture**

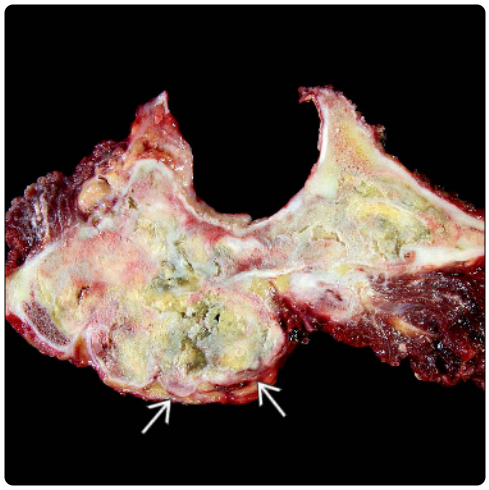


**Soft Tissue Recurrence**

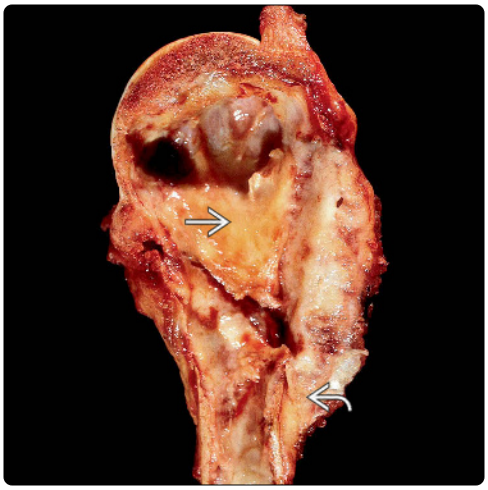


**(Left)** *A large GCT fills and expands the medial femoral condyle and extends into the metaphysis. It has caused a transarticular fracture that originates near the intercondylar notch. The tumor is red-tan and relatively well circumscribed.* **(Right)** *Recurrent GCT forms a large mass in skeletal muscle lying beneath scarred subcutaneous fat and skin. It has a yellow and red-brown cut surface, is well demarcated, and is partially surrounded by a shell of reactive bone.*

**Treatment Effect**



**Sarcomatous Change**

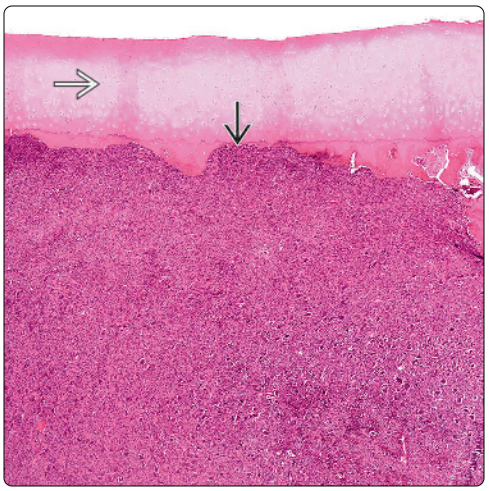


**(Left)** *GCT status post treatment with denosumab shows a variegated cut surface. The tan-yellow (necrosis) tumor has broken through the cortex medially, forming a large soft tissue mass.* **(Right)** *Sarcoma arising in a proximal humerus was previously curetted for a conventional GCT of bone. The tan-white tumor involves the medullary cavity and extends into the neighboring soft tissues.*

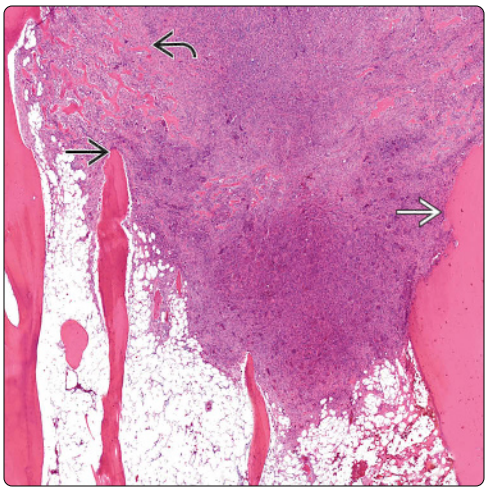


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### Tumor Eroding Subchondral Bone Plate

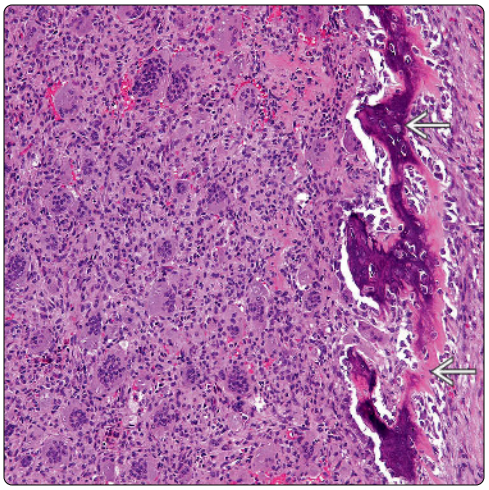


### Advancing Edge of Tumor

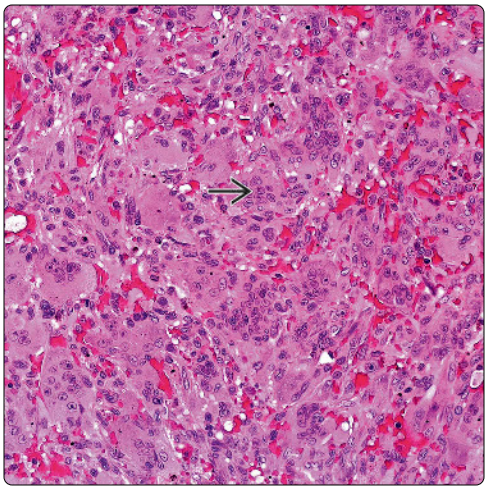


**(Left)** *Low-power view shows a GCT involving the epiphysis of a long tubular bone. The solid tumor is cellular, well defined, and erodes the subchondral bone plate adjacent to the tide mark cartilage. The articular cartilage is intact.* **(Right)** *The intramedullary proximal aspect of a GCT of bone abuts the ends of residual bony trabeculae and scallops the cortex. The tumor is solid and contains reactive woven bone peripherally.*

### Peripheral Rim of Reactive Bone

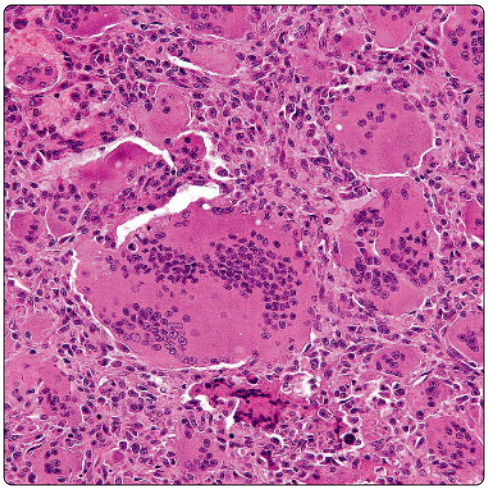


### Hemorrhage and Many Giant Cells

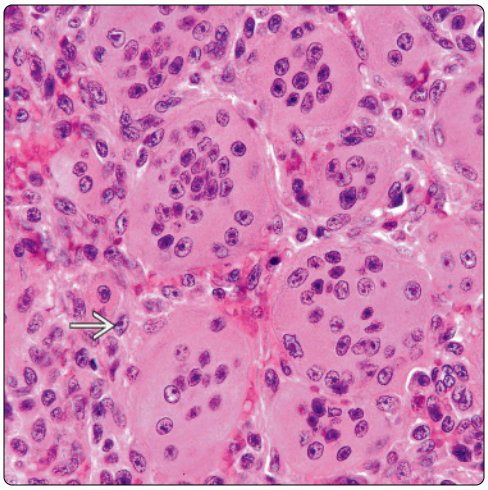


**(Left)** *This GCT of bone has destroyed the cortex and displaced the periosteum, which has produced a thin shell of reactive woven bone rimmed by osteoblasts. The tumor is cellular with many osteoclast-type giant cells.* **(Right)** *This typical GCT is composed of an admixture of neoplastic mononuclear cells and numerous, evenly distributed osteoclast-type giant cells. Note the abundant extravasated red blood cells, which are common in GCTs.*

### Very Large Giant Cells



### Large Osteoclast-Like Giant Cells

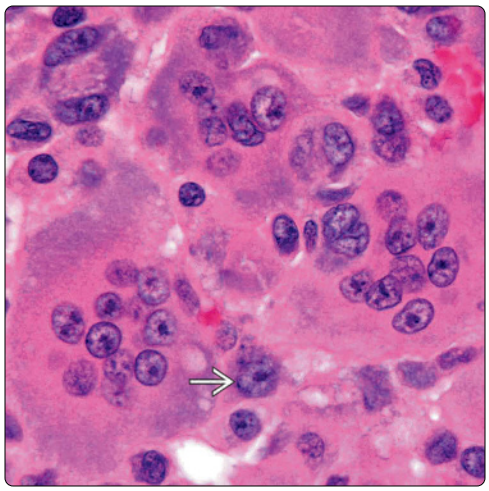


**(Left)** *Gigantic osteoclast-type giant cells in a GCT are seen. These cells may be formed by the fusion of smaller osteoclast-type giant cells. It is unusual to see this type of giant cell in other primary bone tumors.* **(Right)** *This typical GCT is composed of many large multinucleated osteoclast-type giant cells. The giant cells contain numerous nuclei that are similar in appearance to the nuclei in the neoplastic mononuclear cells.*

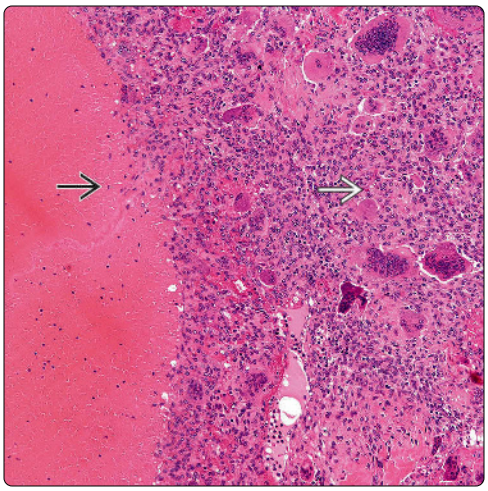


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### Similar Nuclear Morphology

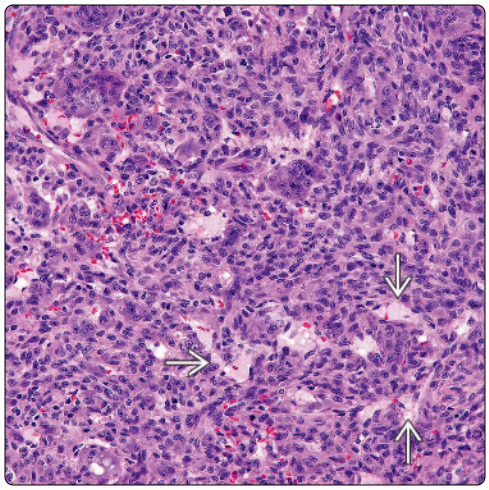


### Hemorrhagic Cystic Change

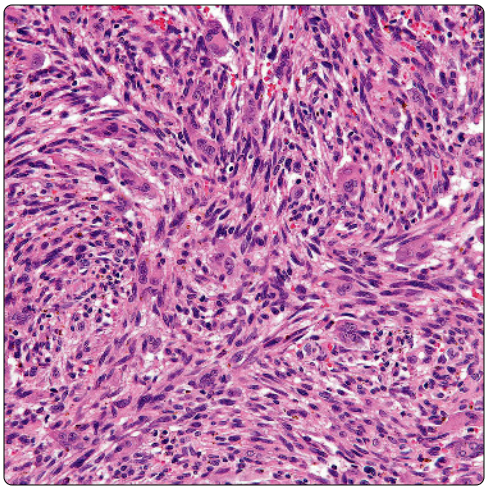


**(Left)** *High-power view of the osteoclast-type giant cells shows that the nuclei have a finely dispersed chromatin pattern and small to moderately sized purple nucleoli. The mononuclear cells ➡ have the same nuclear features.* **(Right)** *A GCT with secondary cystic changes contains areas of typical GCT ➡ composed of mononuclear cells and multinucleated osteoclast-type giant cells and blood-filled cystic spaces ⇨. Sometimes the cyst wall can mimic an aneurysmal bone cyst.*

### Staghorn Vascular Pattern

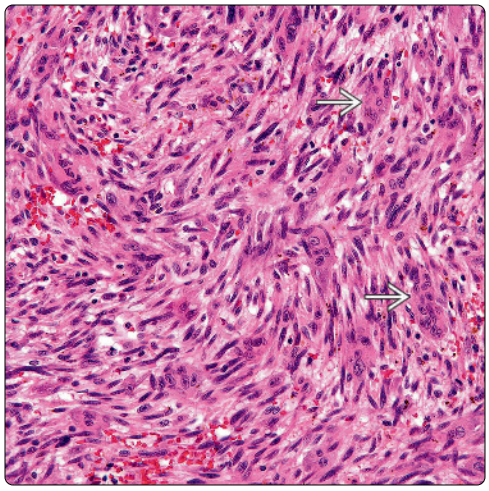


### Storiform Pattern

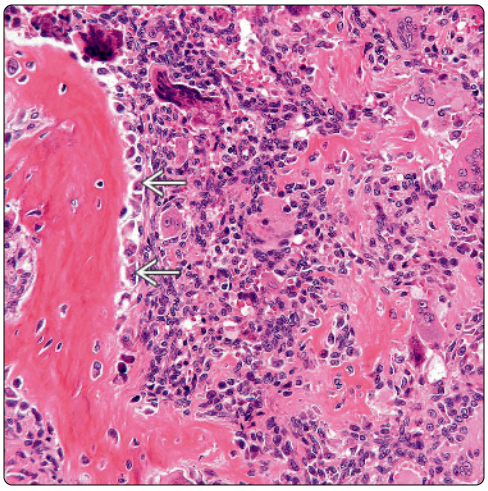


**(Left)** *A GCT shows a prominent vasculature. There are scattered giant cells, sheets of mononuclear cells, and a prominent vascular tree ➡ that has a hemangiopericytoma-like pattern.* **(Right)** *Many GCTs contain spindle cell areas that resemble a benign fibrous histiocytoma. The plump and bland spindle cells are arranged in a storiform pattern, and the diagnosis of GCT of bone should be considered in a bone tumor with a prominent storiform pattern.*

### Fascicles of Spindle Cells



### Reactive Woven Bone

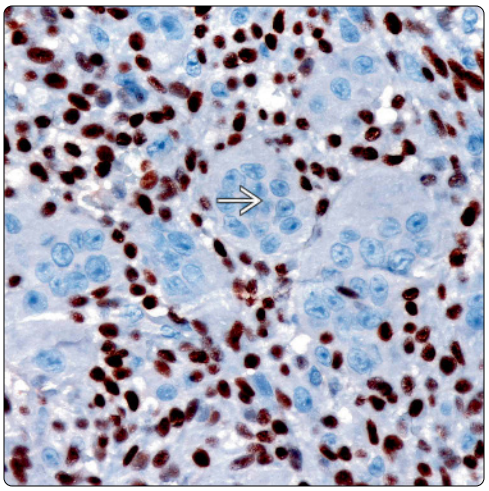


**(Left)** *Spindle cell component in a GCT has a benign fibrous histiocytoma-like appearance. The spindle cells are arranged in a storiform pattern with scattered giant cells ➡.* **(Right)** *This GCT of bone demonstrates prominent reactive woven bone formation. The bone is lined by osteoblasts ➡ and ranges from well-formed trabeculae to a lace-like pattern, which can cause confusion with a giant cell-rich osteosarcoma.*

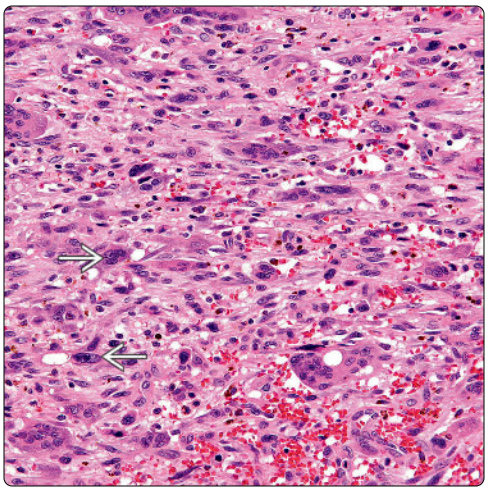


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### Mononuclear Cells Staining With p63

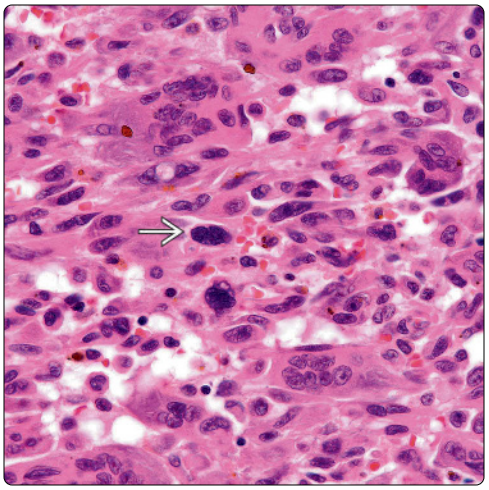


### Benign vs. Malignant

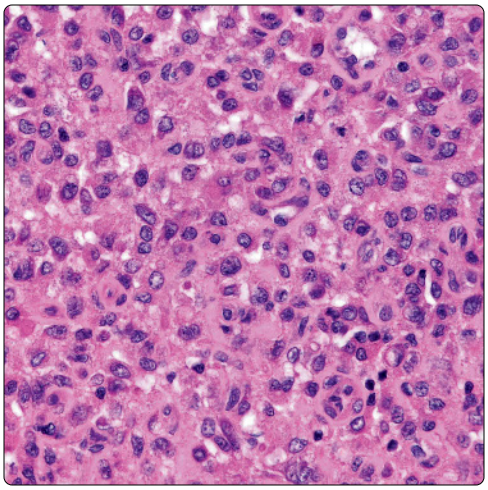


**(Left)** *A GCT of bone stained with p63 shows strong nuclear staining of the mononuclear cells but not of the multinucleated osteoclast-type giant cells. Other giant cell-rich tumors, such as chondroblastoma, may also express this antigen.* **(Right)** *Atypical GCT of bone with scattered mononuclear cells demonstrates nuclear hyperchromasia and enlargement. The degree of atypia is worrisome for, but not diagnostic of, malignancy; tumors with this morphology should be extensively sampled.*

### Hyperchromasia and Nucleomegaly

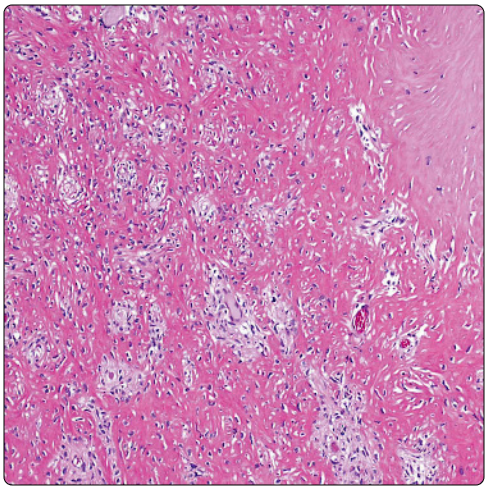


### Loss of Giant Cells

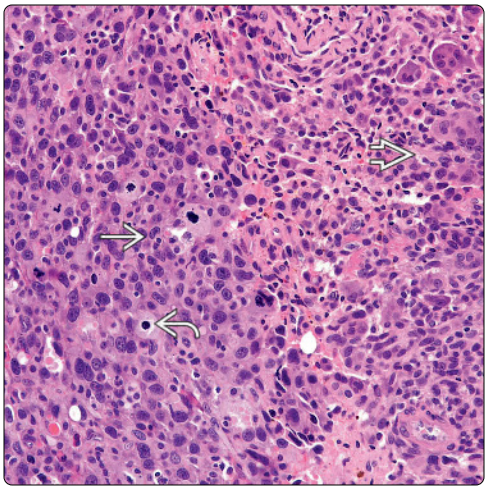


**(Left)** *An atypical GCT shows scattered mononuclear cells with hyperchromatic and enlarged nuclei. Their presence raises the possibility of sarcoma, which usually shows more atypical cells and an infiltrative growth pattern.* **(Right)** *This GCT of bone is from a patient treated with denosumab, an antibody targeting receptor activator of NF-κB (RANK) ligand. The giant cells are no longer present, leaving behind a population of ovoid and spindle-shaped mononuclear cells.*

### Treatment Effect



### Sarcomatous Transformation



**(Left)** *The effects of successful treatment of GCT with a RANK ligand inhibitor is necrosis of the tumor and replacement by reactive fibrosis and abundant reactive woven bone. The presence of the bone can raise the differential diagnosis of osteosarcoma.* **(Right)** *Malignant transformation of a GCT of bone shows an area of typical GCT adjacent to a malignant component composed of sheets of severely atypical mononuclear cells with numerous mitotic figures.*



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# Brown Tumor

KEY FACTS

## TERMINOLOGY

- Bone tumor composed of nonneoplastic reactive tissue that occurs in setting of primary, secondary, or tertiary hyperparathyroidism

## ETIOLOGY/PATHOGENESIS

- Parathyroid hormone binds to receptors on surface osteoblasts, which express receptor activator of NF-kB (RANK) ligand
- RANK ligand binds to RANK on osteoclast precursors, inducing formation of osteoclasts

## CLINICAL ISSUES

- Usually develops during 3rd and 4th decades of life but can arise in anyone with hyperparathyroidism
- Females affected more frequently
- May be solitary or multiple
- Presents as mass that may be painful
- Treat underlying hyperparathyroidism

## IMAGING

- Expansile, lytic lesions

## MACROSCOPIC

- Reddish-brown hemorrhagic mass with lobular architecture produced by fibrous septa that may contain reactive bone

## MICROSCOPIC

- Lobules composed of admixture of plump fibroblasts, extravasated red blood cells, hemosiderin-laden macrophages, and scattered osteoclast-type giant cells that frequently cluster around areas of hemorrhage
- Lobules separated by septa containing trabeculae of reactive woven bone

## DIAGNOSTIC CHECKLIST

- Nodules of benign spindle cells with hemorrhage and associated clusters of osteoclast type giant cells

**Multiple Brown Tumors**



*AP radiograph of the hip shows multiple lytic lesions of variable size and shape in all of the visualized bones. The lesions are well defined and lack sclerotic margins and internal matrix.*

**Brown Tumor of Rib**



*Rib is expanded by a brown tumor. The mass is reddish brown, well circumscribed, and delineated into multiple nodules by numerous septa. The surrounding cortex is thinned but intact.*



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## TERMINOLOGY

### Synonyms

- Brown tumor of hyperparathyroidism

### Definitions

- Bone tumor composed of nonneoplastic reactive tissue that occurs in setting of primary, secondary, or tertiary hyperparathyroidism

## ETIOLOGY/PATHOGENESIS

### Developmental Anomaly

- Develops as complication of hyperparathyroidism
  - Usually parathyroid hyperplasia or adenoma
    - Rarely caused by parathyroid carcinoma
- Parathyroid hormone binds to receptors on surface of osteoblasts, which express receptor activator of NF-κB ligand (RANKL)
  - RANKL binds to receptor activator of NF-κB (RANK) on osteoclast precursors, inducing formation of osteoclasts
- Hemorrhage and hemosiderin deposition associated with osteoclastic bone resorption, in addition to microfractures, gives tumor its brown color

## CLINICAL ISSUES

### Epidemiology

- Age
  - Usually develops during 3rd and 4th decades of life but can arise in anyone with hyperparathyroidism
- Sex
  - Females affected more frequently

### Site

- May be solitary or multiple
- Usually arises in pelvis, ribs, clavicles, and extremities
- Atypical locations include sphenoid sinus, vertebral column, and cricoid cartilage

### Presentation

- Mass that may be painful

### Laboratory Tests

- Elevated parathyroid hormones and calcium

### Treatment

- Treating underlying hyperparathyroidism
- Surgery in selected cases

### Prognosis

- Related to underlying cause of lesion
- Successful treatment of hyperparathyroidism leads to reduced osteoclastic activity, and brown tumor eventually regresses and fills in with newly deposited bone

## IMAGING

### Radiographic Findings

- Expansile, lytic lesion with occasional intralesional trabeculations
- Tumor margins may be well defined or indistinct
- Other radiographic features of hyperparathyroidism often present
- Radiographic differential diagnosis may include giant cell tumor of bone, metastatic carcinoma, multiple myeloma

### MR Findings

- Variable signal intensity

### Bone Scan

- Increased uptake of radionuclide

## MACROSCOPIC

### General Features

- Well-circumscribed, reddish-brown hemorrhagic mass with lobular architecture
- Thins and expands cortex
- Large, blood-filled cysts may develop (osteitis fibrosa cystica)
- Peripheral shell of reactive bone may be present

## MICROSCOPIC

### Histologic Features

- Lobules of plump fibroblasts, extravasated red blood cells, hemosiderin-laden macrophages, and osteoclast-type giant cells that cluster in areas of hemorrhage
  - Lobules separated by septa composed of reactive fibrous tissue and trabeculae of woven bone
- Adjacent bone show evidence of hyperparathyroidism
  - Dissecting osteitis with osteoclasts resorbing centers of bony trabeculae
  - Cortical cutting cones composed of osteoclasts expanding haversian systems

## DIFFERENTIAL DIAGNOSIS

### Giant Cell Tumor of Bone

- Diagnostic areas not composed of spindled fibroblasts
- Nuclei of mononuclear cells of giant cell tumor are morphologically identical to those of osteoclasts
- Osteoclast-type giant cells are evenly distributed

### Solid Aneurysmal Bone Cyst

- Can histologically look similar to individual lobules in giant cell reparative granuloma
- Aneurysmal bone cyst does not demonstrate lobular growth pattern seen in brown tumor
  - May be indistinguishable on small biopsy specimens

### Giant Cell Reparative Granuloma

- Can have very similar morphologic features
- Brown tumor has much more lobulated architectural growth pattern
- Features of hyperparathyroidism in surrounding bone are not present

### Metastatic Carcinoma

- Multiple brown tumors can mimic metastatic carcinoma radiographically

## SELECTED REFERENCES

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2. Bassler T et al: Osteitis fibrosa cystica simulating metastatic tumor. An almost-forgotten relationship. Am J Clin Pathol. 100(6):697-700, 1993



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**Lytic Tumor**



**Pathological Fracture**

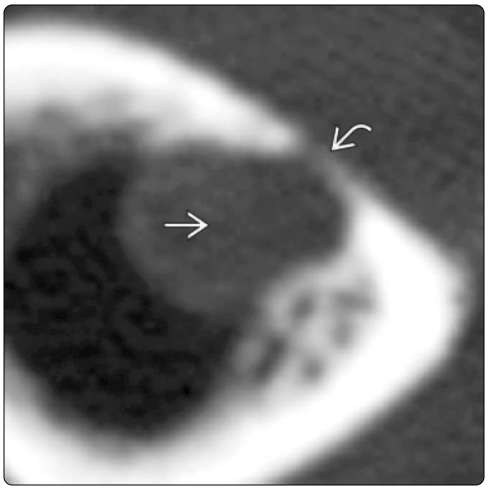


**(Left)** *Brown tumor expands the distal tibial diametaphysis. The lesion is well circumscribed, lytic, and thin but does not transgress the surrounding cortex. The uninvolved bone and fibula exhibit subtle osteopenia.* **(Right)** *A pathologic fracture is present and extends through a lytic lesion in the distal humeral shaft. The lesion is oval and has a well-defined margin. The bone is severely osteopenic, which is common in severe hyperparathyroidism.*

**Destructive Tumor**



**Mass-Eroding Corex**

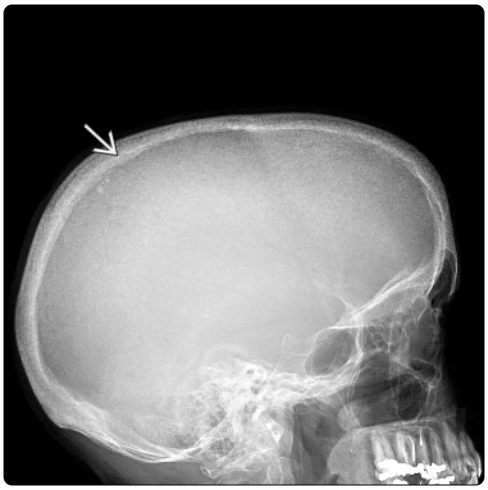


**(Left)** *A multiloculated brown tumor is present in the ilium. The proximal part of the lesion has expanded through the cortex and extends into the iliacus muscle but is confined by a thin shell of periosteal reactive bone. The tumor is multinodular and compartmentalized by septa.* **(Right)** *Axial CT of a brown tumor in the tibia shows that the mass has soft tissue density. The eccentric, well-circumscribed tumor erodes and attenuates the overlying cortex.*

**Hyperparathyroidism**



**Hyperparathyroidism Involving Skull**

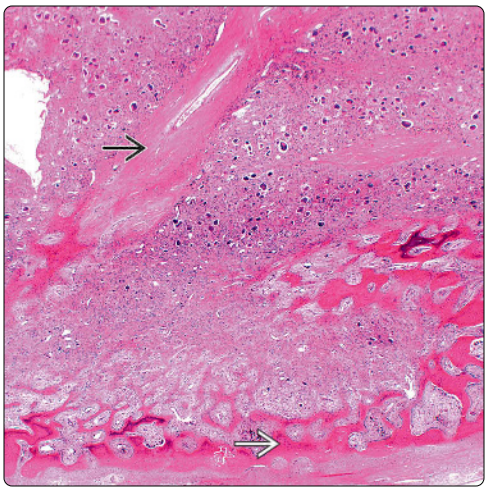


**(Left)** *Radiograph of the hand shows severe osteopenia with resorption of tufts, subperiosteal resorption of the proximal and middle phalanges, and a lytic lesion in the 5th proximal phalanx. These findings are characteristic of hyperparathyroidism. Narrowing of the metacarpophalangeal and interphalangeal joints is also noted.* **(Right)** *Lateral view of the skull shows significant osteoporosis producing a salt and pepper appearance of the cortices that is typical of hyperparathyroidism.*

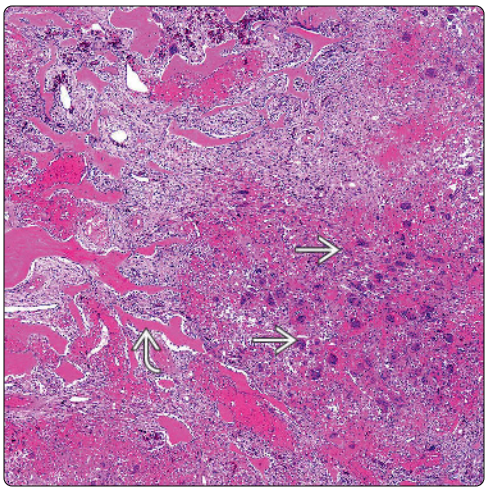


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### Reactive Woven Bone

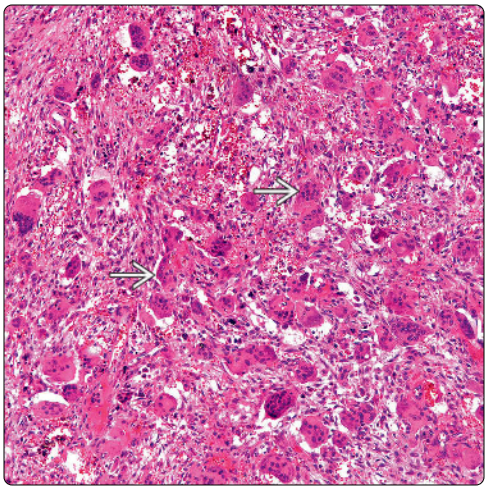


### Nodule of Tumor

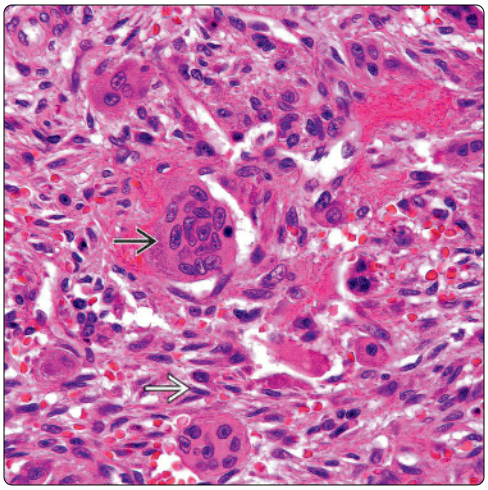


**(Left)** *Brown tumor is surrounded by a rim of reactive subperiosteal woven bone. The tumor is compartmentalized by septa composed of fibrous tissue and reactive bone. The tumor is mainly solid, hemorrhagic, and hypercellular.* **(Right)** *Nodule of brown tumor is partially surrounded by trabeculae of reactive bone. The solid tumor is hemorrhagic and contains osteoclasts that tend to cluster with scattered areas of extravasated red blood cells.*

### Many Osteoclast-Type Giant Cells

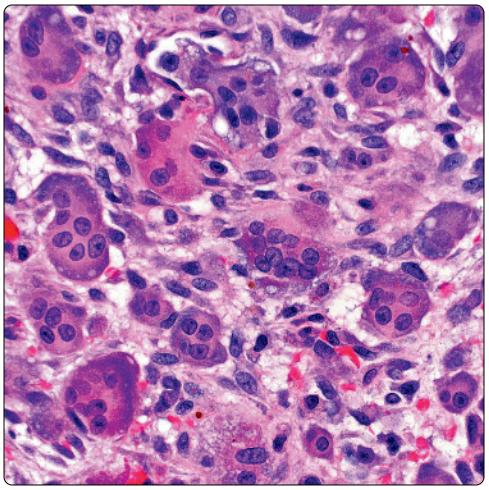


### Spindle Cells in Stroma

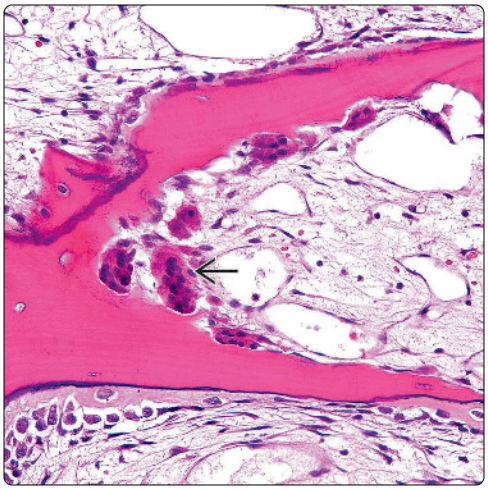


**(Left)** *Brown tumor is hypercellular and composed of spindle cells that have features suggestive of fibroblasts admixed with numerous scattered osteoclasts and extravasated red blood cells.* **(Right)** *Brown tumor is hypercellular and composed of fibroblasts arranged in short fascicles with many scattered osteoclasts that tend to cluster in areas of hemorrhage. The spindle cells are cytologically bland and may demonstrate occasional mitoses.*

### Limited Number of Nuclei



### Dissecting Osteitis



**(Left)** *The osteoclasts in brown tumor usually contain fewer nuclei than those present in giant tumor of bone. The nuclei in the osteoclasts are oval and different in appearance from those of the spindle cells, a feature that helps distinguish the lesion from giant cell tumor of bone.* **(Right)** *Trabecula of bone is shown being resorbed by osteoclasts. The osteoclasts bore down the center of the bone. This is known as "dissecting osteitis" and is characteristic of hyperparathyroidism.*



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# Giant Cell Reparative Granuloma

KEY FACTS

## TERMINOLOGY

- Uncommon giant cell-rich tumor with predilection for craniofacial skeleton and small bones of appendicular skeleton

## CLINICAL ISSUES

- Arises in jaw bones or small tubular bones of hands and feet
- Mandible more common than maxilla
- In small bones of hands and feet, can involve phalanges, metacarpals, and metatarsals, as well as carpal and tarsal bones
- Pain and swelling
- Usually treated with simple curettage
- Tumors are benign and do not metastasize

## IMAGING

- Well demarcated and radiolucent
- Often trabeculated or multiloculated, especially in large tumors
- Forms radiolucent, expansile lesion in bones of hands and feet

## MACROSCOPIC

- Red-brown
- Hemorrhagic

## MICROSCOPIC

- Consists of spindled fibroblasts and collagenous stroma with areas of hemorrhage and numerous multinucleated, osteoclast-type giant cells
- Giant cells tend to be arranged in small clusters around areas of hemorrhage and usually contain ≤ 12 nuclei
- Mitotic figures usually few in number

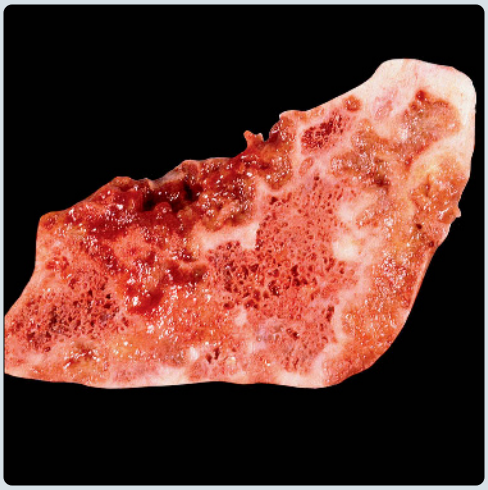
## DIAGNOSTIC CHECKLIST

- Spindle cells with scattered foci of hemorrhage admixed with osteoclast-type giant cells

**Oval Lytic Mass**

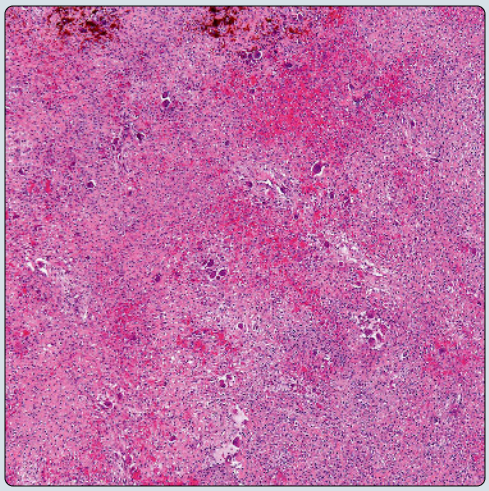


**Giant Cell Reparative Granuloma**

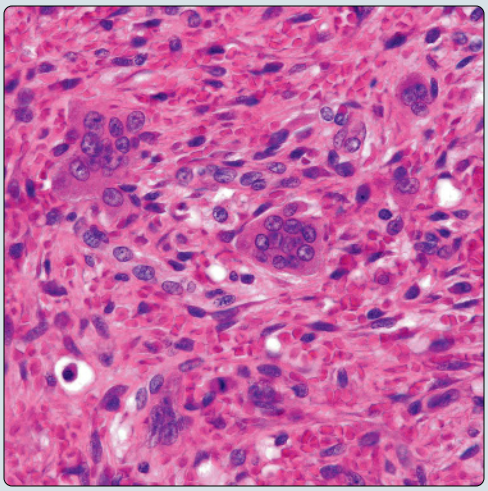


**(Left)** *Radiograph shows a giant cell reparative granuloma (GCRG) in the posterior portion of the body of the mandible. The tumor is expansile, lytic, well circumscribed, and surrounded by a thin layer of reactive bone.* **(Right)** *Partial mandibular resection from a patient with cherubism shows a lobulated, red-brown hemorrhagic mass with lobules separated by reactive bone formation.*

**Scattered Foci of Hemorrhage**



**Giant Cells Admixed With Blood**



**(Left)** *GCRG has scattered foci of hemorrhage throughout the tumor. The giant cells usually cluster around the aggregates of red blood cells.* **(Right)** *Scattered osteoclast-type giant cells are associated with areas of hemorrhage in GCRG. The osteoclast-type giant cells tend not to have > 12 nuclei.*



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## TERMINOLOGY

### Synonyms

- Giant cell reaction
- Giant cell granuloma

### Definitions

- Benign giant cell-rich tumor with predilection for craniofacial skeleton and small bones of appendicular skeleton
  - Some tumors in short tubular bones may be solid aneurysmal bone cyst
    - Solid aneurysmal bone cyst can be identified by rearrangement of *USP6*
- Tumors morphologically identical to giant cell reparative granuloma (GCRG) are present in cherubism
  - Cherubism is autosomal dominant disorder
  - Maps to chromosome 4p16.3
  - Mutation in *SH3BP2* gene produces disease
  - Patients have multiple bilateral tumors
    - Tumors develop in maxilla and mandible
    - Cosmetic bulging of cheeks produces cherub facies
  - Similar tumors may occur in patients with neurofibromatosis type 1 and Noonan syndrome
    - Neurofibromatosis has mutation in *NF1* gene
    - Noonan syndrome has mutation in *PTPN11* gene
    - Jaw lesions in patients with Jaffe-Campanacci syndrome are histologically similar to GCRG

## CLINICAL ISSUES

### Epidemiology

- Age
  - Usually develop during 1st and 2nd decades of life
    - Patients are typically between 10-15 years old
    - Patients with tumors in jaws are often younger than those with tumors in short tubular bones
- Sex
  - F:M = ~ 2:1

### Site

- Arises in jaw bones (mandible > maxilla) or short tubular bones of hands and feet
  - Rarely arises in long bones, pelvis, or spine
- In hands and feet, can involve phalanges, metacarpals, metatarsals
  - Carpal and tarsal bones are less frequently involved

### Presentation

- Pain
- Swelling
- Mass-producing cosmetic deformity
- Displacement of teeth
- Rarely incidentally discovered on radiographs
- Some jaw lesions may be very large and rapidly growing

### Treatment

- Curettage
- Surgical removal via curettage or en bloc resection of lesion combined with radiation or drug therapy may be indicated in surgically inaccessible lesions
  - Skull base
    - Tumors in anatomic sites that are difficult to access surgically, such as skull base, may be treated with drug therapy and radiation
      - Rank ligand inhibitors and calcitonin have been utilized

### Prognosis

- After curettage, lesion usually heals and defect becomes ossified
- Can locally recur
  - Usually adequately controlled by repeat curettage
    - Some jaw lesions are locally aggressive with rapid growth and recurrence

## IMAGING

### Radiographic Findings

- Oval, well demarcated, and radiolucent
- Often trabeculated or multiloculated
  - Large tumors have septations oriented at right angles to cortex
- Adjacent teeth more frequently displaced than resorbed
- Cortex usually intact
- No periosteal reaction
  - Often expanded and thinned
- Forms radiolucent, expansile lesion in bones of hands and feet
  - Can involve
    - Diaphysis
    - Metaphysis
    - Epiphysis
    - Entire length of bone
- Margins may be sclerotic

### MR Findings

- Hypointense or isointense on both T1- and T2-weighted images
- Displays extent of tumor

### CT Findings

- Expanded, lytic lesion with septations
  - Similar to muscle in density
- Hypovascular to avascular
- Demonstrates substance and borders of tumor

## MACROSCOPIC

### General Features

- Bloody and red-brown
- Friable
- Gritty
- Sometimes secondary cystic change is present

## MICROSCOPIC

### Histologic Features

- Composed of spindled fibroblasts and collagenous stroma with areas of hemorrhage and numerous multinucleated, osteoclast-type giant cells
  - Mass of tissue is well circumscribed
  - Tumor does not permeate preexisting cancellous or cortical bone



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- Giant cells tend to be arranged in small clusters around areas of hemorrhage
  - Giant cells usually contain ≤ 12 nuclei
    - Smaller than those in giant cell tumor of bone
  - Less numerous than in giant cell tumor of bone
- Secondary histological findings frequently present
  - Scattered lymphocytes
  - Hemosiderin deposits
  - Reactive woven bone rimmed by osteoblasts
  - Small, blood-filled spaces
- Mitotic figures are usually few in number
  - Mitoses have normal structure
- Necrosis is uncommon

## ANCILLARY TESTS

### Immunohistochemistry

- No immunohistochemical features are helpful in making diagnosis of GCRG or differentiating it from other giant cell-rich lesions
  - p63(+) in many GCRGs, as in other giant cell-rich lesions

### Genetic Testing

- Sporadic tumors do not have genetic aberration
- Patients with underlying syndrome have associated genetic abnormality

## DIFFERENTIAL DIAGNOSIS

### Brown Tumor of Hyperparathyroidism

- GCRG can closely resemble brown tumor of hyperparathyroidism
  - Brown tumor usually contains more fibrous septa that subcompartmentalize tumor into multiple lobules
  - Adjacent bone may demonstrate features of hyperparathyroidism
  - Metabolic studies show calcium metabolism disorder
- Patients with GCRG should be considered to have appropriate testing to exclude hyperparathyroidism

### Giant Cell Tumor of Bone

- Histologically, giant cell tumor of bone contains numerous large, osteoclast-type giant cells evenly distributed throughout tumor
  - In contrast, giant cells frequently cluster around areas of hemorrhage in GCRG
  - Giant cells in giant cell tumor usually have > 12 nuclei
- Mononuclear cells in GCRG are spindle-shaped and not oval/round as in giant cell tumor of bone
  - Nuclei of mononuclear cells in giant cell tumor of bone are identical to nuclei in osteoclast-type giant cells
    - Not seen in GCRG
  - Mononuclear cells grow in syncytial pattern in giant cell tumor
    - Not present in GCRG
- Both tumors show expression of p63 in mononuclear cells
- Giant cell tumor of bone has mutation in *H3F3A* gene that is not present in GCRG

### Aneurysmal Bone Cyst

- Solid aneurysmal bone cyst histologically resembles GCRG
  - Foci of hemorrhage are less prominent
  - Contains more prominent woven bone trabeculae
- *USP6* gene rearrangement present in aneurysmal bone cyst has not been identified in GCRG of jaw
  - Many tumors in hands and feet often have *USP6* gene rearrangement
    - Therefore, they are examples of solid aneurysmal bone cyst

### Nonossifying Fibroma

- Histologically similar to GCRG
- Has more prominent storiform growth pattern
- Also contains foamy histiocytes and hemosiderin-laden cells
- Arises eccentrically in metaphysis of long tubular bones
  - Very unusual site for GCRG
- Does not contain prominent intratumoral hemorrhage

### Ossifying Fibroma

- Tumor contains matrix as inherent component
  - Woven bone trabeculae
  - Cementum-like deposits
  - Psammomatous calcifications
- Osteoclasts are often associated with matrix
- Intralesional hemorrhage is limited or absent

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Radiolucent mass of jaws
  - May be large, rapidly growing, and locally aggressive

### Pathologic Interpretation Pearls

- Spindle cells with scattered foci of hemorrhage admixed with osteoclast-type giant cells
- Multiple tumors in jaws likely represent cherubism
- Keep hyperparathyroidism high in differential diagnosis

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### Large Giant Cell Reparative Granuloma



### Destructive Tumor



**(Left)** *Coronal CT shows a very large lesion arising from the right maxilla. The lesion is mostly within the maxillary sinus, but the lateral cortex of the maxilla appears destroyed. A large amount of calcification is present.* **(Right)** *GCRG of the maxilla has destroyed the bone and teeth. The expansile, well-circumscribed tumor has a round shape and consists of lucencies that are surrounded by a rim that is ground glass-like in appearance.*

### Lytic Mass in Mandible

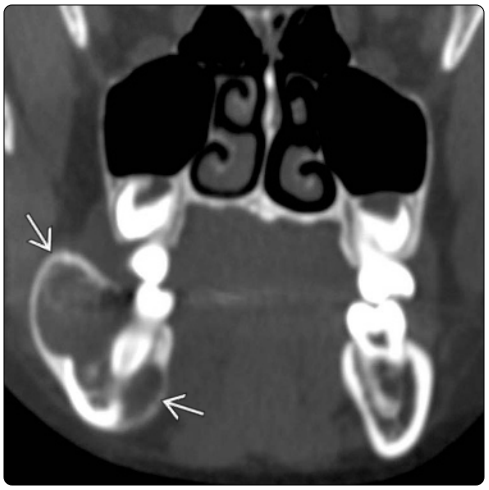


### Expansile Mass



**(Left)** *Panorex image of GCRG of the mandible reveals a well-circumscribed mass that has sclerotic margins. The tumor has eroded the inferior portions of the roots of the neighboring teeth.* **(Right)** *A large, rather posteriorly located lesion of the right mandible is shown. The lesion is solitary and is centered in the medullary cavity. The cortex is expanded and thinned but not destroyed. The teeth are displaced but not eroded.*

### Expansile Tumor



### Lytic and Sclerotic Tumor

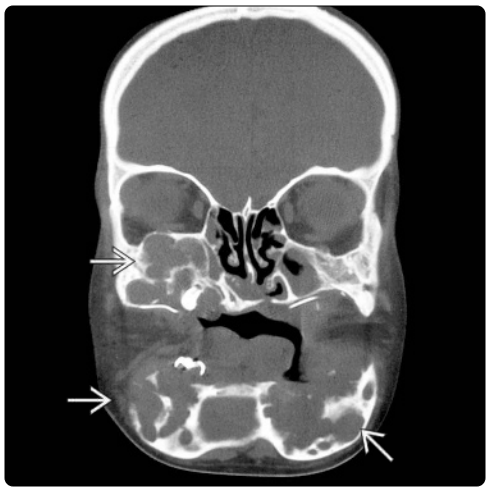


**(Left)** *Coronal CT scan of a GCRG shows a lytic, well-demarcated lesion of the right maxilla. The lesion is multilocular and has expanded the cortex. Close inspection shows ill-defined, fine, cloud-like trabeculations within the lesion.* **(Right)** *GCRG arises in the mandible and expands the bone anteriorly. The tumor is lytic and sclerotic. The sclerosis is caused by reactive bone formation.*



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**Cherubism**

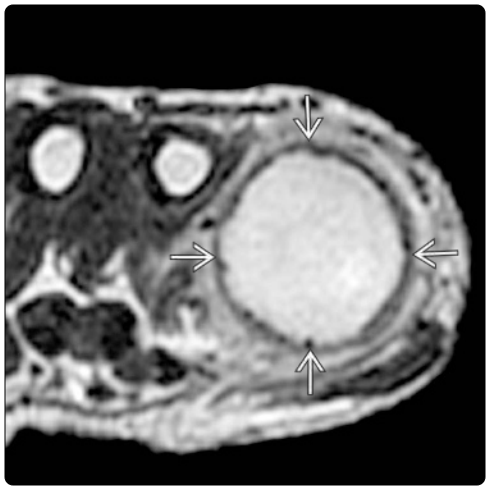


**Low-Attenuation Mass**



**(Left)** *Coronal reformation of CT scan in a patient with cherubism shows bilateral, symmetrical, multifocal lesions of the anterior mandible and maxilla. A few tiny flecks of calcification are seen in the lesions of the left mandible.* **(Right)** *Coronal T1-weighted oblong GCRG presents as a solid mass that has low attenuation. The tumor is surrounded by a thin layer dark intensity bone.*

**Tumor Confined by Periosteal Shell**

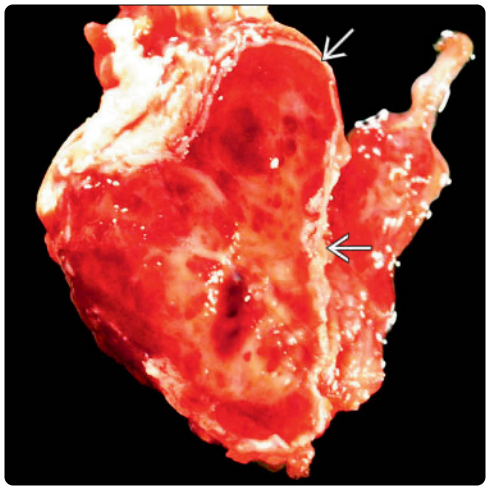


**Giant Cell Reparative Granuloma MR**

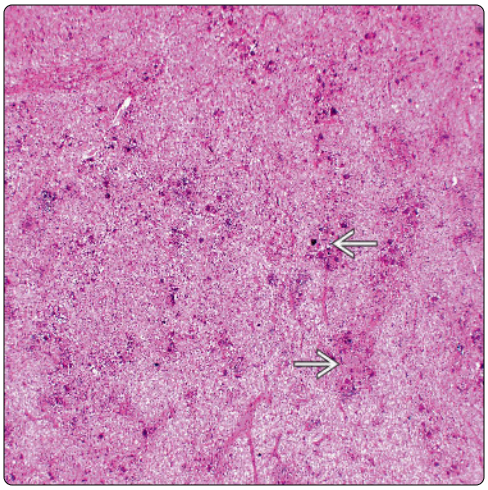


**(Left)** *T1WI, fat-suppressed, contrast-enhanced MR of a GCRG of the hand demonstrates mild contrast enhancement of the lesion. It is well circumscribed but has expanded the bone.* **(Right)** *T1WI, fat-suppressed, contrast-enhanced sagittal MR of a GCRG of the metacarpal shows faint increased signal of the tumor. The cortex is expanded but intact.*

**Gross Specimen**



**Cellular Tumor**

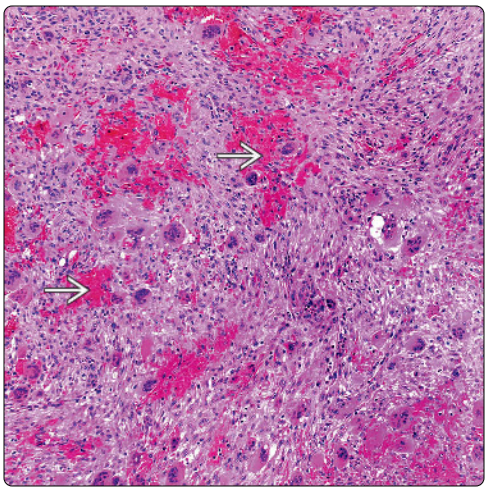


**(Left)** *Resection specimen of a mandibular GCRG demonstrates a tan-red tumor. The tumor is well demarcated and is surrounded by a thin rim of bone.* **(Right)** *Low-power view shows the typical appearance of a GCRG. The tumor is cellular and has areas of stromal hemorrhage. The multinucleated, osteoclast-type giant cells tend to aggregate in these areas.*

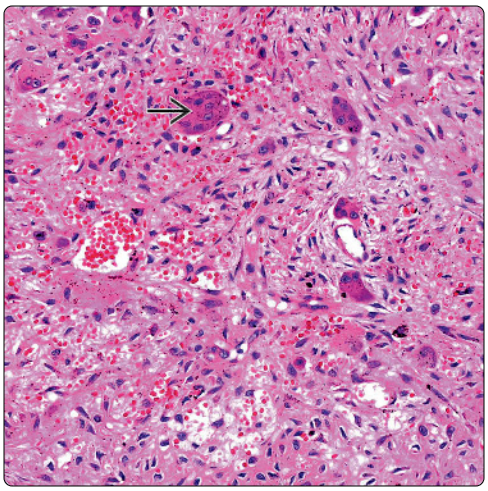


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Foci of Hemorrhage

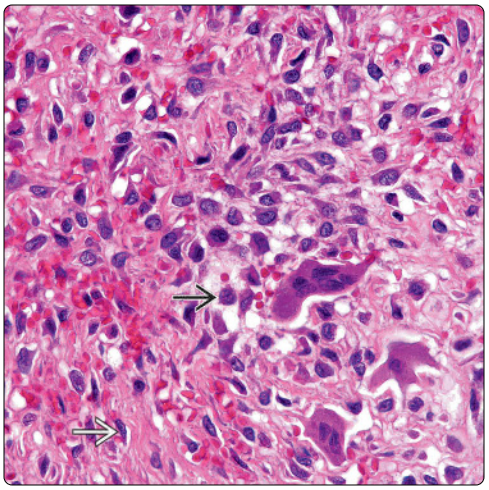


Spindle Cells and Giant Cells

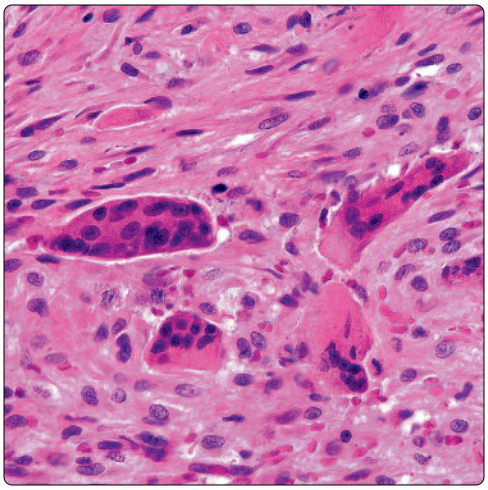


**(Left)** *GCRG contains spindle-shaped stromal cells that are arranged in short fascicles and osteoclast-type giant cells. The giant cells tend to aggregate around areas of stromal hemorrhage ➡.* **(Right)** *This GCRG shows the admixture of stromal cells and osteoclast-type giant cells ⇨. The stromal cells are spindle-shaped and do not demonstrate the same nuclear morphology as the nuclei of the osteoclast-type giant cells, which are also usually smaller and have fewer nuclei than are seen in giant cell tumor of bone.*

Hemorrhage and Giant Cells

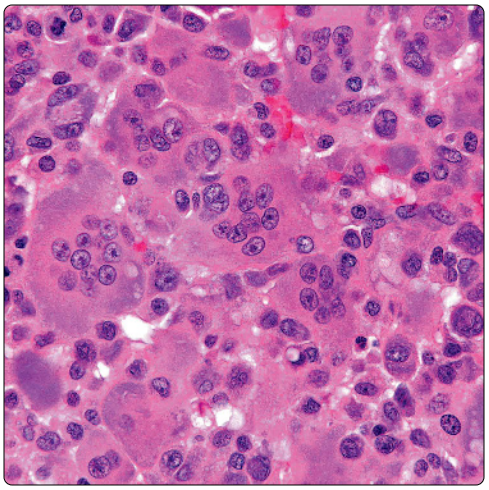


Cherubism

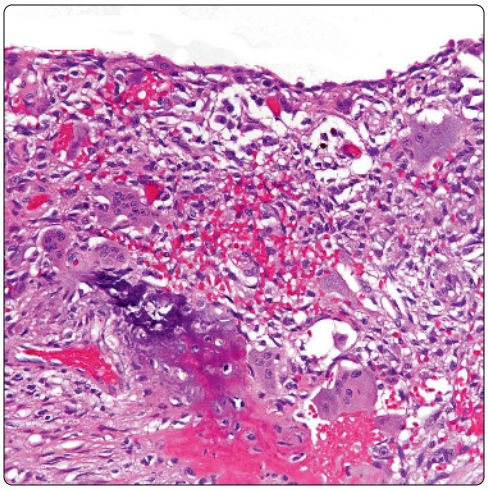


**(Left)** *Extravasated red blood cells are present in the collagenous stroma of the GCRG. The fibroblasts are spindle-shaped ➡ and are adjacent to histiocytes ⇨ and osteoclast-type giant cells.* **(Right)** *High-power view of a tumor in a patient with cherubism shows the characteristic histologic features. The mononuclear stromal cells are spindle-shaped, and the osteoclast-type giant cells form small clusters.*

Giant Cell Tumor of Bone



Aneurysmal Bone Cyst



**(Left)** *Giant cell tumor of bone differs from GCRG in that the mononuclear cells grow in a syncytial pattern and have nuclei that closely resemble those in the osteoclast-type giant cells.* **(Right)** *Aneurysmal bone cyst can resemble GCRG by light microscopy. Helpful features to help distinguish them from one another is the presence of cysts, "blue bone," and lack of clustering of the giant cells around foci of hemorrhage.*



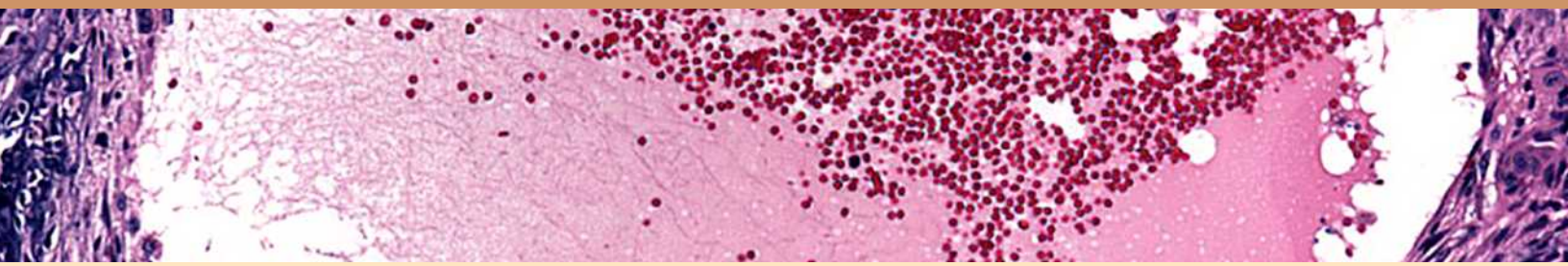
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SECTION 10

# Cystic Lesions of Bone




| | |
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| Epidermoid Inclusion Cyst | **306** |


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# Intraosseous Ganglion

KEY FACTS

## TERMINOLOGY

- Pseudocyst that is filled with viscous mucoid material
- Degenerative changes of adjacent joint should not be present

## CLINICAL ISSUES

- Usually asymptomatic and typically discovered as incidental finding
- May cause chronic pain exacerbated by physical activity
- Commonly develops in subchondral regions of bones of hip, knee, ankle, wrist, and shoulder

## IMAGING

- Eccentric, round to oval, radiolucent with sclerotic margins

## MACROSCOPIC

- Thin-walled cyst filled with translucent gelatinous fluid sharply demarcated from surrounding sclerotic rim of bone
- Curettage specimens may consist of bloody strips of cyst wall and portions of its mucinous contents

## MICROSCOPIC

- Cyst wall lacks true epithelial cell lining and is composed of hypocellular fibrous tissue that contains abundant collagen, identical to its soft tissue counterpart
- Lumen is filled with amorphous basophilic remnants of viscous fluid that may be admixed with red blood cells and scattered inflammatory cells
- Surrounding bone shows rebuttressing and remodeling of trabecula and marrow fibrosis with myxoid change

## TOP DIFFERENTIAL DIAGNOSES

- Fibromyxoma of bone
- Chondromyxoid fibroma
- Subchondral cyst
- Chondrosarcoma

**Intraosseous Ganglion of Knee**



*Intraosseous ganglion of the tibia shows a lucent circumscribed lesion with sclerotic margins in the mid subchondral area. The joint space is preserved with no significant degenerative changes.*

**Gross Photograph of Intraosseous Ganglion**



*Excised intraosseous ganglion from the fibula is composed of 2 locules that are well demarcated. The cyst wall is thin and translucent, and the adjacent bone is focally sclerotic.*



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## TERMINOLOGY

### Abbreviations

- Intraosseous ganglion (IOG)

### Synonyms

- IOG cyst

### Definitions

- Nonneoplastic, fibrous-walled pseudocyst that develops in subchondral regions of bone
- Pseudocyst filled with viscous synovial-like mucoid fluid
- Degenerative changes of adjacent joint should not be present, if significant osteoarthritis is present, then cyst is best considered subchondral

## ETIOLOGY/PATHOGENESIS

### Uncertain

- Possibly degenerative in origin

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Unknown; usually asymptomatic and incidentally discovered
- Age
  - Usually diagnosed during mid adulthood
- Sex
  - Males are affected slightly more frequently than females at ratio of ~ 1.2:1

### Site

- Commonly develops in subchondral regions of bones of hip, knee, ankle, wrist, and shoulder

### Presentation

- Typically discovered as incidental finding
- Most lesions are clinically silent
- May cause chronic pain exacerbated by physical activity

### Treatment

- Asymptomatic IOG can be observed and does not require surgical intervention
- Painful lesions can be successfully treated with curettage and bone packing

### Prognosis

- Excellent; very low rate of recurrence

## IMAGING

### Radiographic Findings

- Eccentric, round to oval, well defined, radiolucent
- Contains sclerotic margins, sclerotic borders are thin and regular both internally and externally
- No degenerative changes in adjacent joint

### MR Findings

- Cyst fluid has low signal intensity on T1-weighted images and high signal intensity on T2-weighted images
  - Sclerotic margin has low signal intensity; may be mild surrounding marrow edema

### CT Findings

- Well-demarcated lytic lesion with sclerotic margins

### Bone Scan

- May show avid uptake

## MACROSCOPIC

### General Features

- Thin-walled cyst filled with translucent gelatinous fluid, sharply demarcated from surrounding sclerotic rim of bone
- Curettage specimens may consist of bloody strips of cyst wall and portions of its mucinous contents

### Size

- Usually 0.5-1.0 cm in diameter, lesions as large as 2-5 cm are uncommon

## MICROSCOPIC

### Histologic Features

- Identical to its soft tissue counterpart
- Cyst wall lacks true epithelial cell lining and is composed of hypocellular fibrous tissue
- Tissue adjacent to cyst wall may be myxoid with scattered muciphages
- Amorphous basophilic remnants of viscous fluid is present in lumen
  - May be admixed with red blood cells and scattered inflammatory cells, including histiocytes
- Surrounding bone shows rebuttressing and remodeling of trabecula and marrow fibrosis with myxoid change

## DIFFERENTIAL DIAGNOSIS

### Fibromyxoma of Bone

- Can contain myxoid areas but more fibrous areas are also present

### Chondromyxoid Fibroma

- May contain myxoid areas but also shows other characteristic histologic features

### Subchondral Cyst

- Develops in setting of degenerative changes of articular cartilage
  - Although histologically it can be identical to IOG cyst, by definition, IOG cyst should not be associated with significant degenerative changes

### Chondrosarcoma

- Chondrosarcoma with extensive myxoid change might mimic IOG cyst histologically on small biopsy specimen

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Subchondral lytic lesion in absence of degenerative joint changes is characteristic of IOG cyst

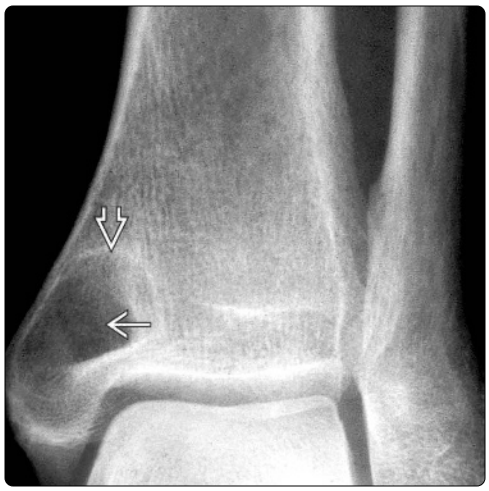
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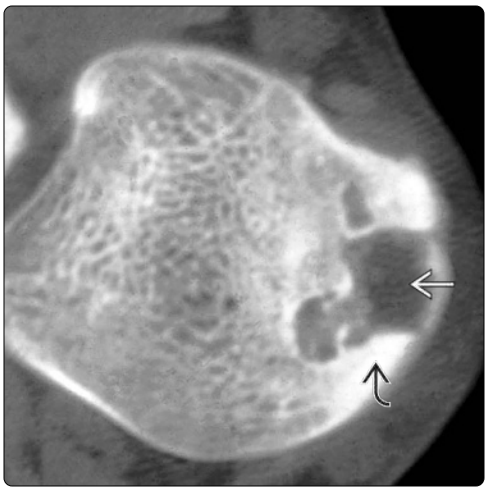


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**Intraosseous Ganglion of Tibia**



**CT Scan of Intraosseous Ganglion**



**(Left)** *Radiograph shows a typical intraosseous ganglion cyst that is arising in a common location. The well-defined lucent lesion involves the distal medial tibia in a subarticular location. The oval lytic lesion has a thin sclerotic margin, and the adjacent joint is unremarkable.* **(Right)** *Axial CT scan of an intraosseous ganglion cyst of the distal tibia shows a heterogeneous and lobulated lesion. The cyst has well-defined margins and adjacent reactive sclerosis.*

**Subchondral Intraosseous Ganglion**

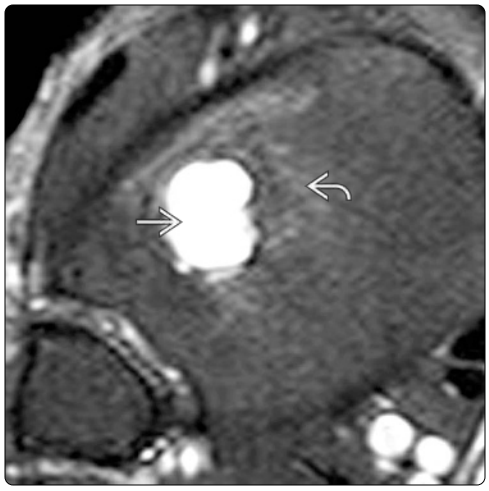


**Fluid-Filled Intraosseous Ganglion**



**(Left)** *Coronal T1-weighted MR shows an intraosseous ganglion cyst in the distal tibia. The cyst is hypointense, and the margins are well defined with surrounding edema. There is a defect in the adjacent tibia raising the possibility of a subchondral cyst.* **(Right)** *Sagittal T2-weighted fat-saturated MR of an intraosseous ganglion shows the hyperintense signal of fluid filling the ganglion with surrounding edema. An internal septum is visible.*

**Fluid Intraosseous Ganglion of Tibia**



**Axial MR of Intraosseous Ganglion**



**(Left)** *Axial T2-weighted MR with fat saturation shows an intraosseous ganglion in the distal tibia. The lesion is hyperintense in signal because of the fluid. Also present is minimal surrounding marrow edema. The neighboring cortex is unremarkable.* **(Right)** *Axial T1-weighted MR of an intraosseous ganglion shows a hypointense round lesion in the distal tibia with a dark rim that represents a sclerotic margin. There is mild edema in the surrounding marrow.*

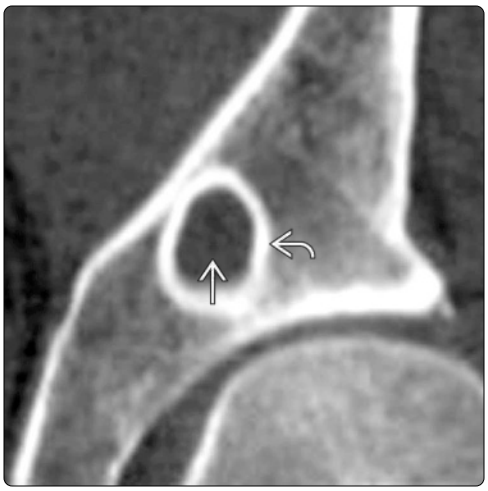


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### Intraosseous Ganglion of Acetabulum

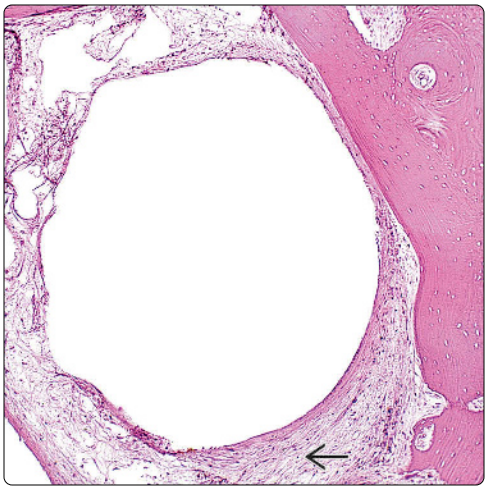


### Intraosseous Ganglion With Sclerotic Rim

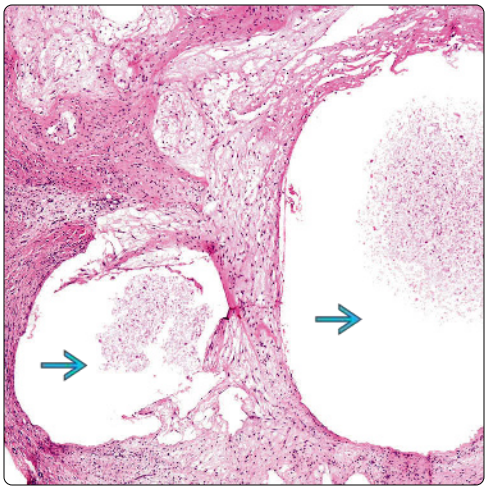


**(Left)** *AP radiograph of the hip shows a well-defined lucent intraosseous ganglion cyst arising in the subarticular acetabular region. The cyst is oval with a thin sclerotic rim. No internal matrix is seen.* **(Right)** *Coronal CT scan shows an intraosseous ganglion cyst arising in the acetabulum demonstrating a round, well-circumscribed, homogeneously lucent lesion with no internal matrix. The margins are sclerotic. The adjacent joint is relatively unremarkable.*

### Light Microscopy of Intraosseous Ganglion

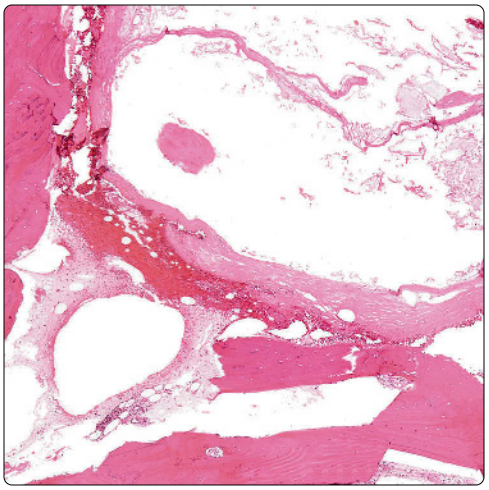


### Intraosseous Ganglion

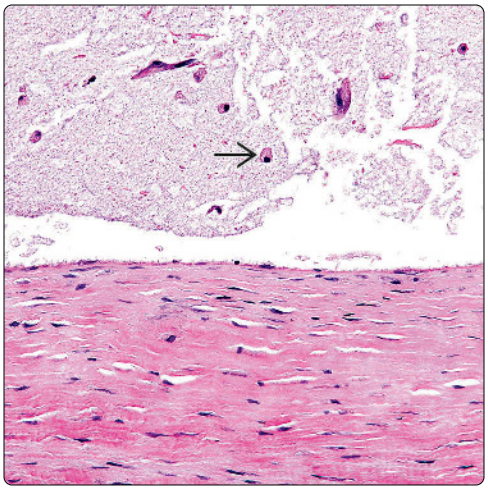


**(Left)** *This intraosseous ganglion is surrounded by bland spindle-shaped fibroblasts embedded in a loose myxoid matrix. The cyst lumen lacks an epithelial cell lining, and the cavity is empty. The surrounding bone is rebuttressed and thickened.* **(Right)** *This intraosseous ganglion shows 2 cystic spaces, both of which are surrounded by bland-looking spindle shaped fibroblasts that are embedded in an extracellular myxoid matrix. The cystic cavities contain granular eosinophilic material. No cyst lining is present.*

### Multiloculated Intraosseous Ganglion



### Wall of Intraosseous Ganglion



**(Left)** *This multiloculated intraosseous ganglion is composed of several cysts involving the medullary cavity. The cysts are surrounded by fibrous tissue. The adjacent lamellar bone is unremarkable.* **(Right)** *The wall of an intraosseous ganglion is composed of a layer of fibrous tissue containing bland fibroblasts embedded in an eosinophilic collagenous matrix. The cyst cavity contains amorphous granular material with scattered histiocytes. No cyst lining is present.*



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# Unicameral Bone Cyst

KEY FACTS

## TERMINOLOGY

- Unicameral bone cyst (UBC): Benign, intraosseous, fluid-filled cyst of unknown etiology

## CLINICAL ISSUES

- Typically occurs in 1st and 2nd decades of life in skeletally immature individuals while growth plates are still open
- Usually arises in appendicular skeleton, especially proximal humerus, proximal femur, and proximal tibia
- Most lesions are asymptomatic
- Painful 2° to pathologic fracture, which occurs in up to 60%
- Most common methods of treatment include curettage, bone grafting, steroid injections, and percutaneous marrow grafting

## IMAGING

- Radiolucent
- Bone may be slightly expanded, but width of cyst is usually not greater than width of epiphyseal plate

## MACROSCOPIC

- Filled with straw-colored or blood-stained serous fluid
- Lined by thin, fibrous wall

## MICROSCOPIC

- Wall consists of thin layer of fibrous tissue composed of scattered banal fibroblasts, collagen fibers, and fibrin deposition
- Cementum-like material is term used for fibrin deposition

## TOP DIFFERENTIAL DIAGNOSES

- Aneurysmal bone cyst
- Ganglion cyst
- Fibrous dysplasia

## DIAGNOSTIC CHECKLIST

- Think UBC for lytic lesion in metaphysis in young person where width is not greater than width of growth plate

**UBC of Humerus**



*A large unicameral bone cyst (UBC) of the humerus extends from the growth plate into the shaft. The cortex is thinned with fine linear structures representing endosteal ridges. A healed fracture is present distally.*

**Translucent Wall**



*Resected long tubular bone with UBC is shown. The cyst wall is translucent with the underlying endosteal surface of the bone visible. The cyst has resulted in expansion of the bone.*

## TERMINOLOGY

### Abbreviations

- Unicameral bone cyst (UBC)

### Synonyms

- Simple/solitary bone cyst

### Definitions

- Benign, intraosseous, fluid-filled, fibrous walled cyst

## ETIOLOGY/PATHOGENESIS

### Developmental Anomaly

- Etiology unknown

## CLINICAL ISSUES

### Epidemiology

- Age
  - Diagnosed in 1st to 2nd decades
    - 80% diagnosed in patients 3-14 years old
- Sex
  - M:F = 2:1

### Site

- Usually arises in appendicular skeleton
  - 60% in proximal humerus
  - 30% in proximal femur
- Cysts in pelvis and calcaneus affect slightly older individuals

### Presentation

- Most are asymptomatic
- Pain secondary to pathologic fracture
  - Occurs in up to 60% of patients

### Treatment

- Ranges from observation to intervention
- Curettage, bone grafting, steroid injections, and percutaneous marrow grafting

### Prognosis

- Local recurrence rate is 10-20%; highest in younger patients
- Spontaneously regresses in most patients

## IMAGING

### Radiographic Findings

- Well-demarcated, lucent, thinned cortex
- Occasional internal trabeculations
  - Trabeculation due to endosteal bony ridges
- Slightly expansile, not greater than epiphyseal plate
- Extends from metaphysis into diaphysis
- Epiphyseal involvement rare
- Centered in medulla, symmetrical
- Early lesions often abut growth plate
  - Skeletal growth lesion becomes centered in shaft
- Some have fractured piece of cortex floating in fluid, producing fallen fragment sign
  - Position change shows free-floating nature of fragment

### MR Findings

- Useful in confirming fluid-filled content
- Demonstrates absence of solid internal components
- May show rim enhancement

### CT Findings

- Well-demarcated, fluid-filled cavity

### Bone Scan

- Increased uptake peripherally
- Decreased uptake centrally
- Can be normal

## MACROSCOPIC

### General Features

- Well delineated with thin fibrous wall
- Filled with straw-colored or blood-stained serous fluid
- Minimal bone expansion

## MICROSCOPIC

### Histologic Features

- Wall lacks epithelial lining (pseudocyst)
  - Thin layer of fibrous tissue composed of fibroblasts, collagen fibers, and fibrin
  - Scattered osteoclasts, hemosiderin, and foamy histiocytes
  - Cementum-like material is collagen and fibrin
- Fibrin can be incorporated into bone by osteoblasts
- Fracture thickens wall with fibroblasts, osteoclasts, hemosiderin, and reactive woven bone
  - Changes caused by fracture can mimic aneurysmal bone cyst

## DIFFERENTIAL DIAGNOSIS

### Aneurysmal Bone Cyst

- When UBC fractures, secondary changes can mimic this diagnosis
- Lytic but more expansile than UBC with fluid-fluid levels on MR
- Cortex is never eccentrically expanded in UBC as in this diagnosis

### Ganglion Cyst

- Usually subchondral location in skeletally mature individuals
- Histologically identical to soft tissue ganglion cyst

### Fibrous Dysplasia

- When prominent cementum-like material present, UBC may mimic this diagnosis

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Think UBC if presentation is lytic lesion in metaphysis in young individual where width is not greater than width of growth plate

### Pathologic Interpretation Pearls

- Membranous fibrous tissue with no lining in curettage

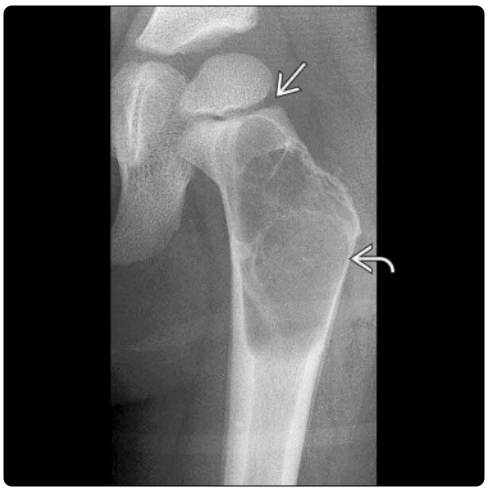
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**UBC of Humerus**



**UBC of Femur**



**(Left)** *Typical UBC is shown in the humerus, the most common location for this lesion. It is several mm from the open growth plate. The metaphysis appears slightly widened, but its diameter does not exceed the width of the growth plate.* **(Right)** *Typical UBC is shown in the proximal femur, the 2nd most common location. The lesion extends to the open growth plate and, although it has thinned the cortex, the profile of the bone is not significantly widened.*

**Well-Demarcated UBC**

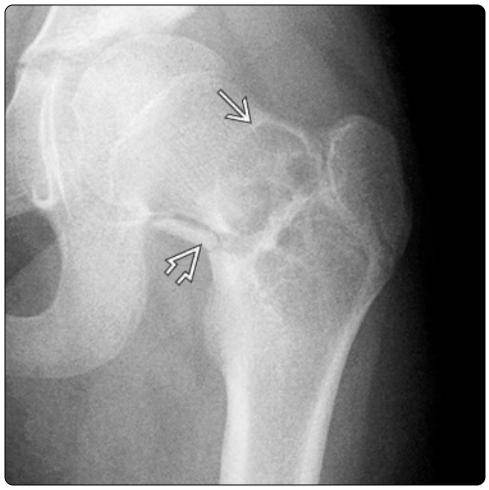


**UBC Involving Diaphysis**



**(Left)** *UBC of the humerus with sharp margins is separated from the open growth plate by several cm of bone. This relationship suggests the bone has undergone considerable growth since the cyst developed.* **(Right)** *UBC of the proximal metaphysis and diaphysis has thinned the cortex, and the bone has undergone a pathologic fracture. A fragment of cortical bone has fallen into the cyst cavity, producing the so-called fallen fragment sign.*

**UBC With Fracture**

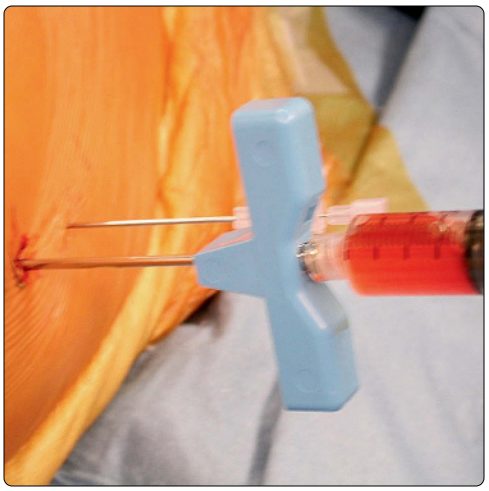


**Fluid-Filled UBC**

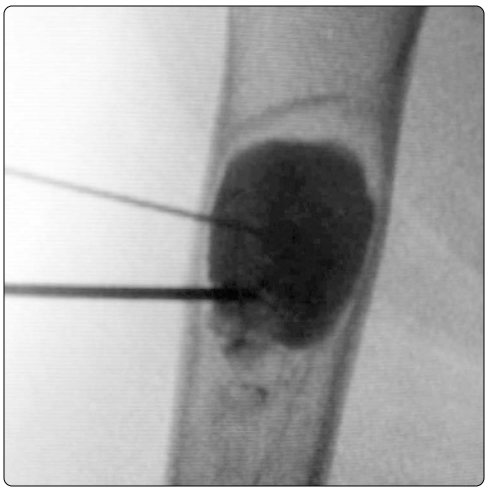


**(Left)** *UBC of the proximal femur has undergone fracture. The oblique fracture has produced a mild angular (varus) deformity. The cyst has well-defined margins, which are sclerotic in the proximal aspect.* **(Right)** *T1 C+ FS MR shows UBC of the proximal femur. Enhancement of the rim is present, but the center shows no enhancement, indicating the absence of blood flow. The wall of this cyst is rather thick.*

**Fluid Contents**



**Cyst Filled With Contrast**



**(Left)** *UBC of the extremity is shown undergoing aspiration. The blood-tinged fluid fills the syringe. A 2nd needle is in place for injection of other materials, such as contrast agents and steroids.* **(Right)** *Intraoperative radiograph shows a UBC of the diaphysis of the long bone that has been aspirated and injected with contrast fluid. The contrast agent completely fills the cyst cavity. Note the oval shape and smooth contour of the lesion. The diameter of the bone is minimally expanded.*

**UBC Filling With Contrast**



**Curettage of UBC**

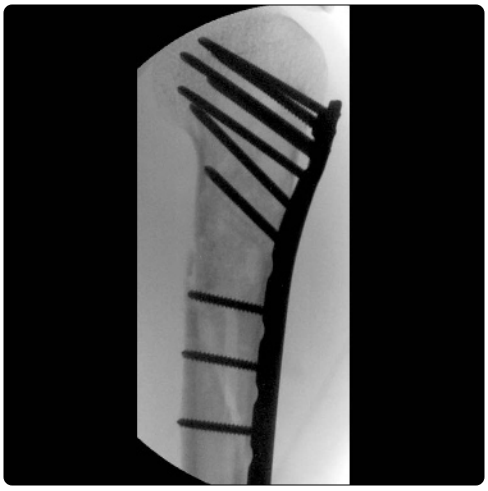


**(Left)** *This is a large UBC that is being filled with contrast material. The tumor extends from the proximal to the mid diaphysis of the humerus. The cyst expands the humerus and has smooth contours.* **(Right)** *Fluoroscopic image of UBC demonstrates a curette placed within the cavity. The curette is used to scrape off the lining of the cyst, which should be submitted for pathologic examination.*

**Large Cyst Filled With Bone Packing**



**UBC Pathologic Fracture**

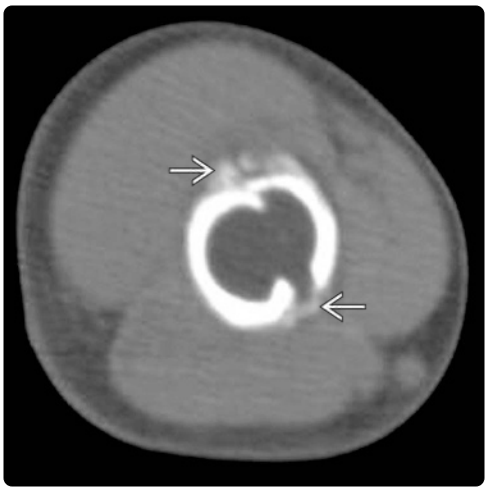


**(Left)** *Postoperative radiograph shows a large UBC of the proximal humerus that has been treated with curettage and packed with bone chips. The cyst has expanded the bone and has resulted in an angular deformity secondary to remote fracture.* **(Right)** *A large UBC produced a pathological fracture that is treated with a metal plate and screws to provide stability for healing.*

**UBC of Diaphysis With Pathologic Fracture**



**CT Scan of Fractured UBC**



**(Left)** *UBC of the humeral shaft with a large pathologic fracture is shown. Presumably this cyst has been present for quite a while, allowing time for the growth plate to become distant from the cyst. The cyst is ovoid and has well-circumscribed margins.* **(Right)** *Axial CT scan shows a UBC arising in the diaphysis of the humerus. There has been a previous fracture with subperiosteal callus formation. The fluid has a soft tissue density, and the contour of the cyst is smooth.*

**UBC With Displaced Fracture**



**Treated UBC**

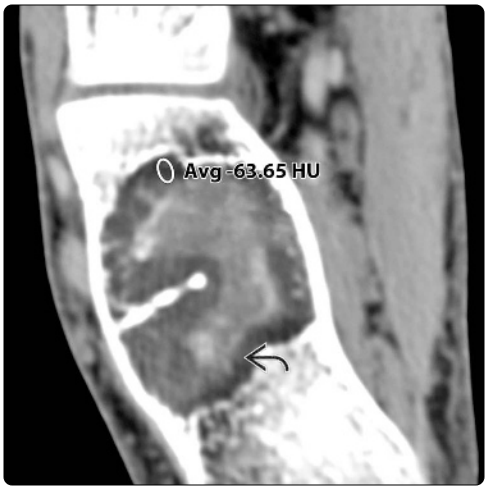


**(Left)** *There is a infratrochanteric fracture seen in the left proximal femoral shaft. The fracture is located at the site of a multiloculated cystic lytic lesion measuring ~ 5.5 cm in diameter that was a UBC on histology.* **(Right)** *Fractured UBC was treated with curettage, bone grafting, sideplate and screw fixation. Radiograph demonstrates continued bone filling in the proximal aspect of the bone cyst.*

**Fluid-Filled UBC of Calcaneus**

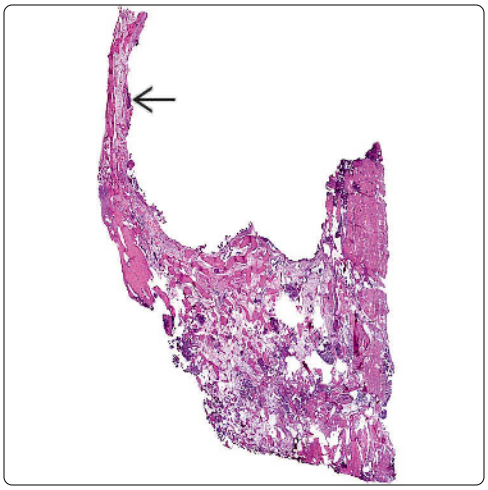


**Low-Attenuation Values**

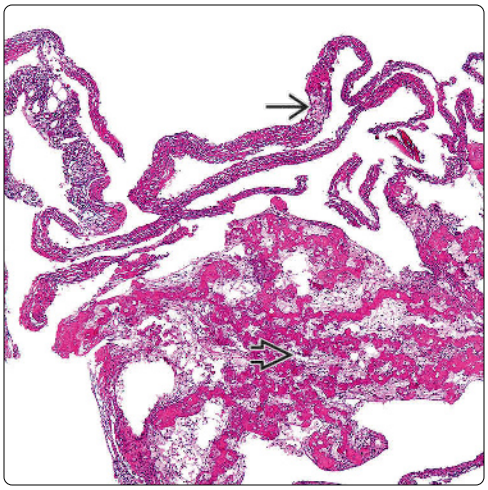



**(Left)** *Typical unicameral cyst of the calcaneus demonstrates uniform, very high signal intensity on this T2 STIR MR. This feature demonstrates the uniformity of the fluid-filled cavity.* **(Right)** *CT scan of a unicameral bone cyst of the calcaneus shows that the periphery has very low attenuation values (-64 HU). This indicates fatty replacement of the bone cavity around the cyst, which has retracted away from the bone. The margins are well delineated.*

### Thin Layer of Fibrous Tissue

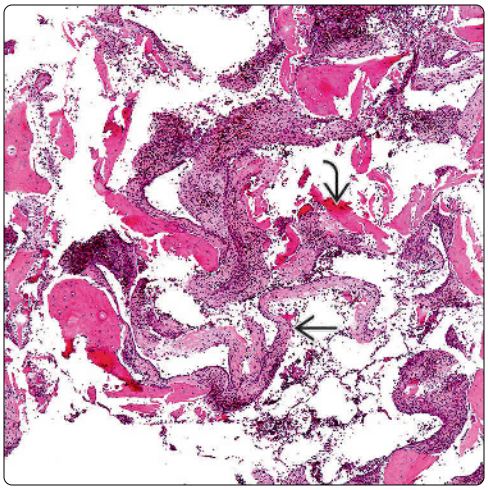


### Cementum-Like Material

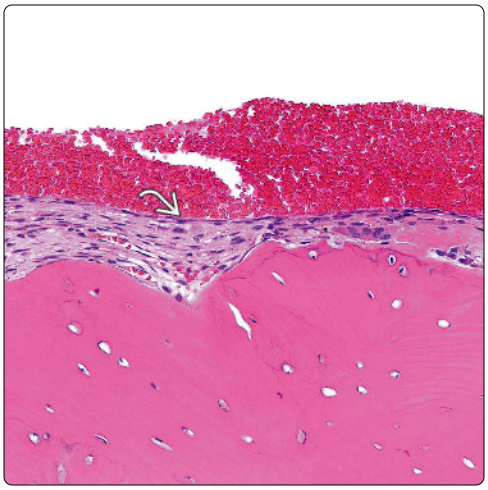


**(Left)** *Thin long bone resected for UBC is shown. The cyst has well-circumscribed margins, has thinned the cortex, and the distal end is bounded by intramedullary reactive bone. The cyst lining is composed of a thin layer of fibrous tissue ⇨.* **(Right)** *A curettage specimen of a unicameral bone cyst shows that the wall of the cyst is composed of thin strips of attenuated fibrous tissue ⇨. A portion of the specimen is more solid and contains abundant eosinophilic, cementum-like material that represents organized fibrin ⇨.*

### Curetted UBC

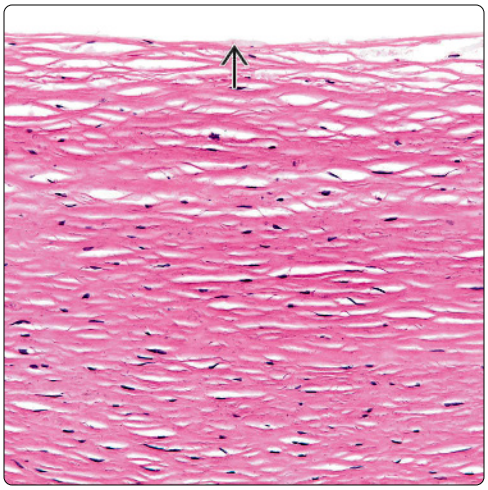


### Wall of UBC

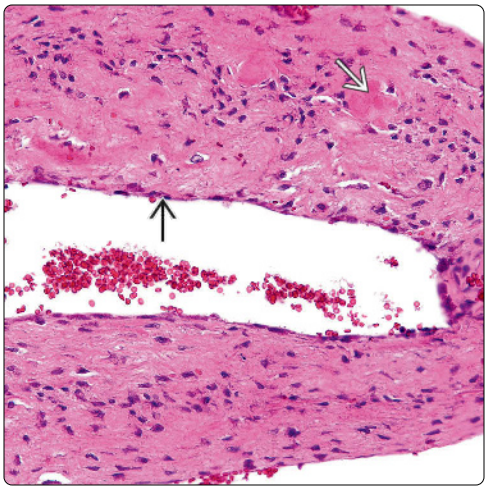


**(Left)** *A curettage specimen from a UBC shows the fragmented wall ⇨ admixed with pieces of bone ⇨. The cyst wall is thin and is composed of fibrous tissue.* **(Right)** *UBC with hemorrhage in the cystic cavity is shown. The cyst wall is composed of spindled fibroblasts and collagen. Note that fibroblasts line the surface ⇨ of the cyst wall, mimicking a true epithelial cyst lining. The underlying endosteal surface of the cortex has an undulating contour.*

### Fibrous Wall of UBC

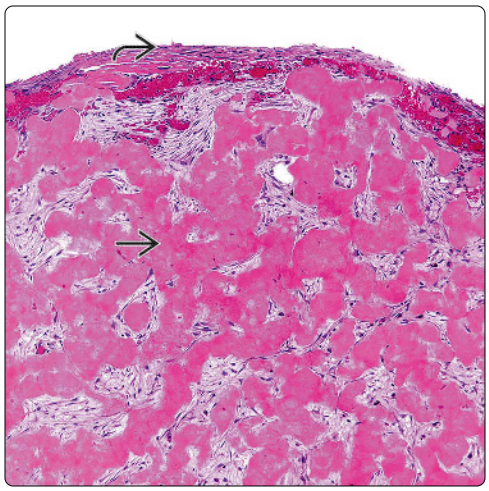


### Fibrous Wall of UBC

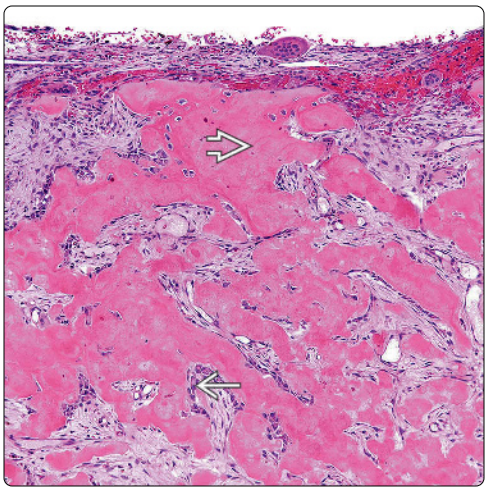


**(Left)** *The wall of a UBC can vary in thickness. In this case, it is thickened and composed of bland fibroblasts enmeshed in abundant collagen, which are oriented parallel to the cyst lumen ⇨.* **(Right)** *Fragment of a wall of a UBC shows fibroblasts ⇨ lining the luminal surface mimicking synovium. The cyst wall contains fibroblasts, collagen, and small amounts of fibrin ⇨.*

### Cementum-Like Material in Wall

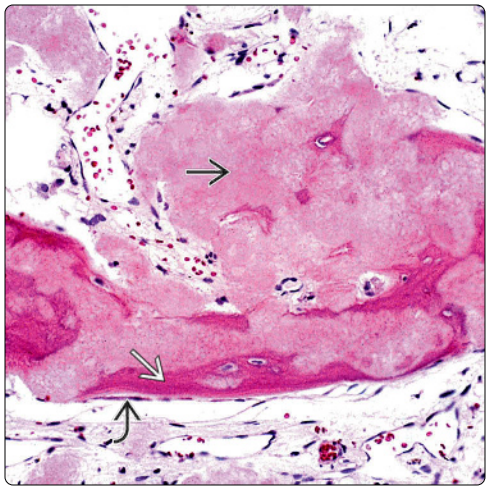


### Bone Deposition in Wall

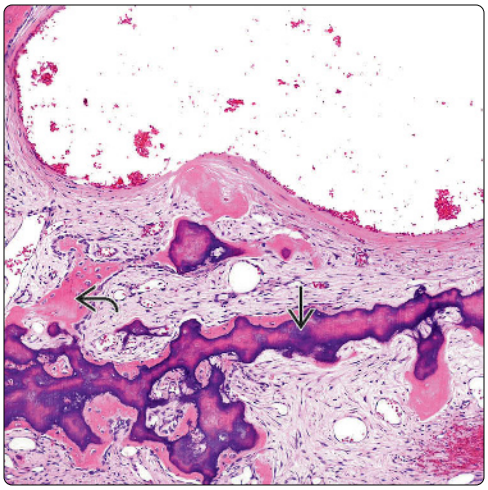


**(Left)** *The wall of a UBC is distorted by abundant intramural fibrin. Fibrin is commonly seen in the walls of UBC and can histologically mimic cementum and neoplastic bone. The luminal portion is lined by a thin layer of fibroblasts.* **(Right)** *Wall of a UBC thickened by abundant fibrin is shown. The pattern of fibrin can mimic cementum and, in this case, manifests as interconnecting linear structures that are rimmed in areas by osteoblasts beginning to deposit bone on its surfaces.*

### Bone Deposition on Surface

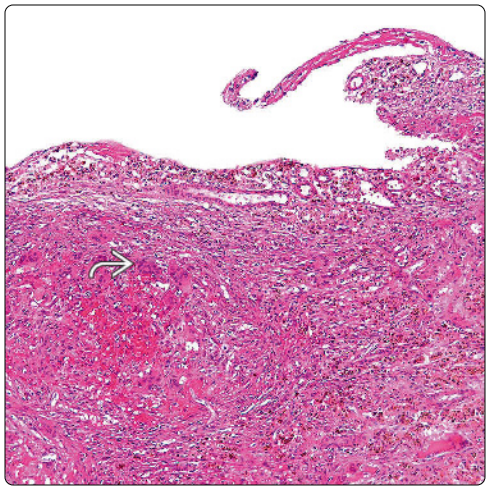


### Ossification in Wall

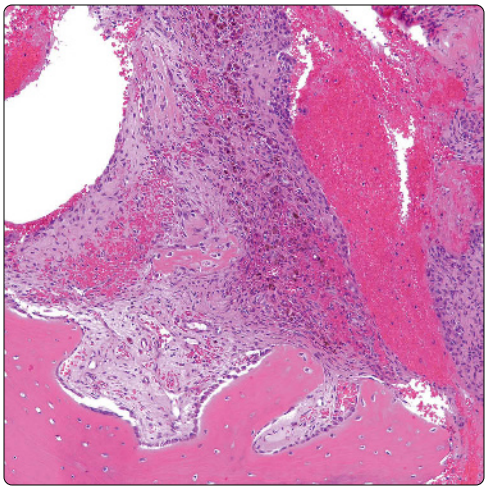


**(Left)** *High-power view of a portion of the wall of a UBC demonstrates fibrin that is acting as the scaffolding for newly formed bone. The bone is rimmed by flattened osteoblasts.* **(Right)** *Lumen of UBC contains scattered red blood cells and are largely confined by the cyst wall. Within the cyst wall, fibrin and collagen have undergone mineralization and ossification.*

### Mimicking Aneurysmal Bone Cyst

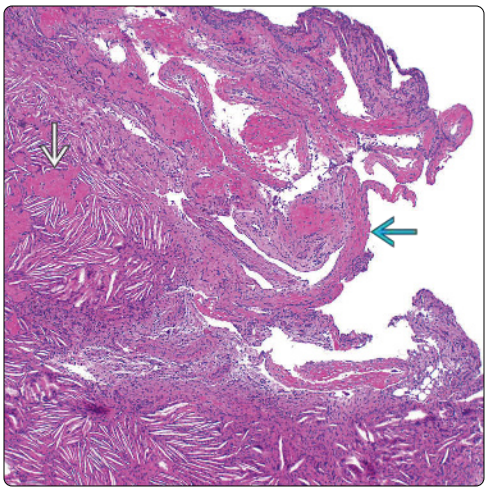


### Fractured UBC

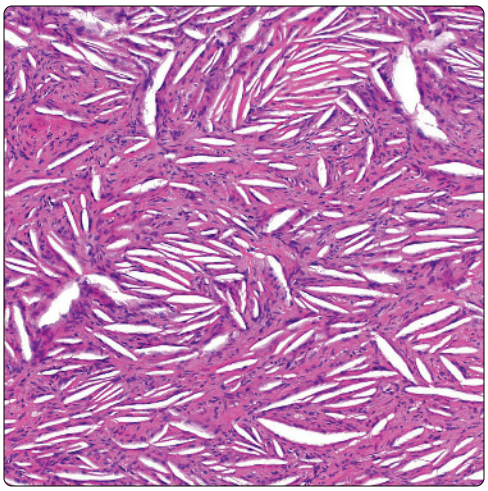


**(Left)** *UBC that has undergone fracture, resulting in reactive changes in the cyst wall, is shown. The wall is markedly thickened by hemorrhage, scattered osteoclast-type giant cells, and reactive fibroblasts. In this situation, the cyst wall may mimic that of an aneurysmal bone cyst.* **(Right)** *The changes associated with pathological fracture cause thickening of the cyst wall, which can mimic that of an aneurysmal bone cyst. The changes include hemorrhage, fibrosis, hemosiderin deposition, and reactive woven bone formation.*

Cholesterol Clefts

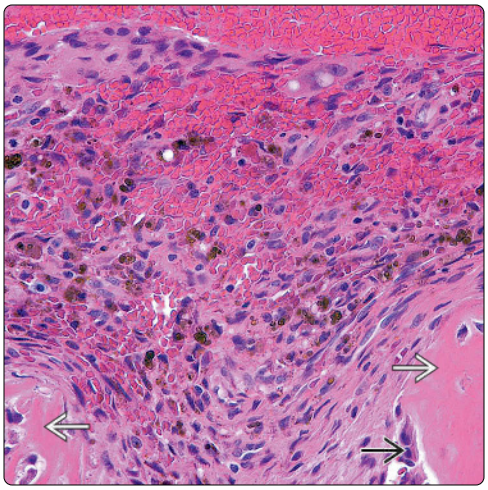


Cholesterol Clefts

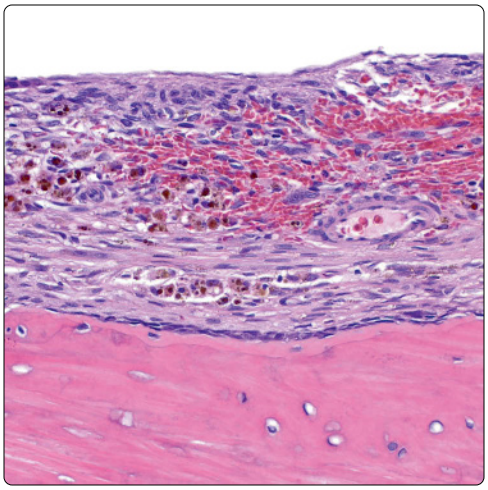


**(Left)** *UBC arising in the calcaneus is shown. The cyst lining is composed of attenuated fibrous tissue ⇨. The wall of the cyst contains organized fibrin ➡ and numerous cleft-like spaces (cholesterol clefts).* **(Right)** *A higher power view shows the cleft-like cholesterol deposition. Although this is a rare finding, it has been described in unicameral bone cysts arising in the calcaneus.*

Fractured UBC

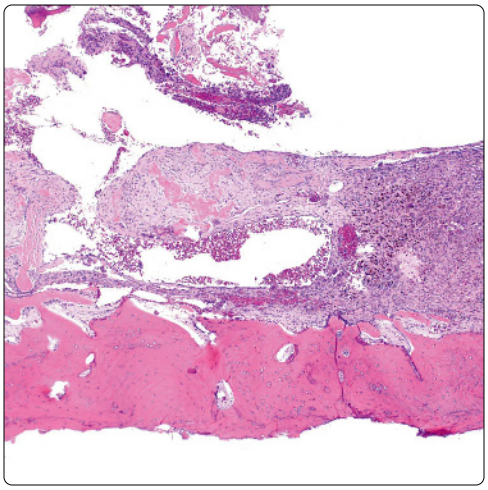


Wall of UBC With Hemorrhage

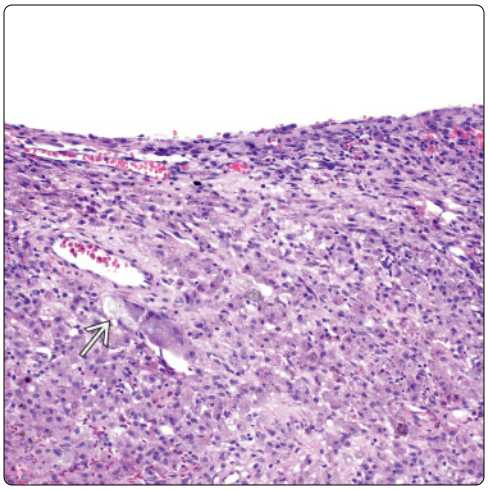


**(Left)** *Fractured UBC shows that the lumen is filled with hemorrhage (top). The cyst wall is thickened by abundant hemosiderin, reactive fibroblasts, and woven bone ➡ that shows prominent osteoblastic rimming ⇨.* **(Right)** *Pathological fracture results in reactive changes that can obscure the cyst wall. The wall in this case is expanded by hemorrhage, hemosiderin deposition, and neovascularization. Notice the prominent osteoblasts lining the adjacent bone.*

Recurrent UBC



Debris in Recurrent UBC



**(Left)** *The wall of a recurrent UBC often shows secondary changes that cause diagnostic challenges. The cyst wall is thickened by reactive fibroblasts, bone, and numerous histiocytes that contain hemosiderin and debris introduced by treatment.* **(Right)** *The wall in this recurrent UBC is significantly thickened by a dense infiltrates of histiocytes that contain hemosiderin. The crystalline material ➡ is remnants from material injected into the cyst as a part of the treatment.*

# Aneurysmal Bone Cyst

KEY FACTS

## TERMINOLOGY

- Destructive, expansile benign tumor with blood-filled cystic spaces
- Classified into primary and secondary variants

## ETIOLOGY/PATHOGENESIS

- Cytogenetic and molecular studies document presence of t(16;17)

## CLINICAL ISSUES

- 80% develop in 1st and 2nd decades of life
- Common sites of involvement
  - Metaphysis of long bones of upper and lower extremities
  - Posterior elements of vertebra
- Present with pain and swelling
- Treated with curettage or en bloc resection
- Local recurrence rate of 12-30%

## IMAGING

- Lytic with "blow out" or marked expansion of bone
- Well circumscribed with fluid-fluid levels
- Usually arises eccentrically within or on bone

## MACROSCOPIC

- Multiple blood-filled cystic spaces separated by thin, tan-white septa

## MICROSCOPIC

- Blood-filled cystic spaces
- Cyst wall composed of spindle cells with scattered osteoclast-like giant cells and reactive woven bone

## TOP DIFFERENTIAL DIAGNOSES

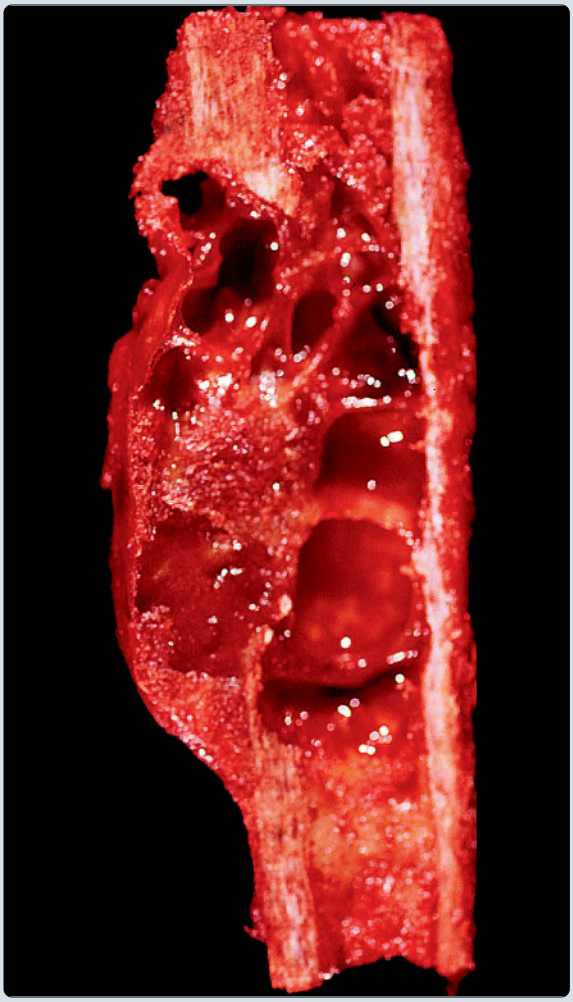
- Giant cell reparative granuloma
- Telangiectatic osteosarcoma
- Secondary aneurysmal bone cyst

**ABC of Ulna**



*Radiograph of an aneurysmal bone cyst (ABC) shows a large eccentric diaphyseal tumor of the ulna extending into the soft tissues that is demarcated by a rim of reactive bone.*

**Numerous Cystic Spaces**



*An ABC arising in the diaphysis of the fibula consists of hemorrhagic cystic spaces with thin fibrous septa. The cyst has broken through the cortex and extended into adjacent soft tissue.*

## TERMINOLOGY

### Abbreviations

- Aneurysmal bone cyst (ABC)

### Definitions

- Destructive, expansile benign neoplasm of bone characterized by multiloculated, blood-filled cystic spaces
- ABCs are classified into primary and secondary variants
  - Primary ABC, or ABC not otherwise specified, refers to de novo neoplasm and accounts for ~ 70% of all cases with ABC components
  - Secondary ABC is defined as primary neoplasm that contains areas of secondary hemorrhagic and cystic change that resembles ABC, which develops in background of other types of benign or malignant bone tumors
    - Giant cell tumor, chondroblastoma, fibrous dysplasia, osteoblastoma, and osteosarcoma are most common primary bone tumors that undergo secondary ABC-like change

## ETIOLOGY/PATHOGENESIS

### Neoplasm

- Cytogenetic and molecular studies document presence of t(16;17) in ABC, including solid variant; strong evidence that primary ABC is neoplastic
  - Most common translocation is t(16;17)(q22;p13)
    - Translocation is hypothesized to occur in preosteoblasts
  - Produces fusion of *CDH11-USP6* genes
    - *CDH11-USP6* gene fusion generates chimeric protein
      - Experiments show that protein inhibits maturation of osteoblasts
      - Causes dysregulation of bone morphogenic protein signaling pathway
    - *USP6/TRE17* oncogene is over expressed
  - FISH can be used to detect t(16;17)(q22;p23) and is diagnostic tool
    - ABCs showing only 17p13 rearrangements show rearrangement of *USP6* locus, whereas those that show 16q22 rearrangement show rearrangement of *CDH11* locus only
  - Variant translocations include t(1:17), t(3:17), t(9:17), and t(17:17)(p13;q21)

## CLINICAL ISSUES

### Epidemiology

- Age
  - Affects all age groups with most cases (80%) occurring in 1st and 2nd decades of life
- Sex
  - Equal male:female ratio

### Site

- Metaphysis of long bones of upper and lower extremities
- Posterior elements of vertebra
- Small bones of hands and feet
- Craniofacial skeleton
- May also arise in flat bones, such as pelvic and scapula bones
- Originates in medullary cavity or on surface of bone
  - Usually eccentrically located in bone and tends not to produce symmetrical expansion
- Rarely arises in soft tissue

### Presentation

- Pain
- Swelling
- Limitation of range of motion
- Palpable mass
- Heralding event may be pathological fracture
- Tumors in spine can cause nerve compression and neurologic symptoms

### Treatment

- Aggressive curettage or en bloc resection
  - En bloc resection for very large destructive tumors or tumors involving expendable bone
- There is some indication that denosumab may be effective in treatment
- Some cases have been treated with intralesional steroid or calcitonin injections
- Percutaneous sclerotherapy and selective arterial embolization has produced favorable results
  - Alternative nonsurgical technique for tumors in sacrum and other sites difficult to excise
- Radiation reserved for tumors involving bones of skull base

### Prognosis

- Recurrence rate 12-30%: usually recur shortly after treatment (within 6 months)
  - Growth rate of recurrence can be rapid, leading to clinical concern for malignancy
- Spontaneous regression may occur following incomplete removal
- Rare reports of apparent malignant transformation of ABC have been described
  - Unclear whether these tumors represent malignant transformation or ABC-like change in preexisting sarcoma
- There has been at least 1 reported cases of ABC that metastasized

## IMAGING

### Radiographic Findings

- Lytic with internal linear trabeculations
  - Often has well-circumscribed, thinly sclerotic margins
  - Trabeculations caused by endosteal ridges as tumor causes resorption of portions of cortex
- Expansile
  - Expansion may be marked producing cosmetic deformity
  - Asymmetric in relation to bone
- Usually arises eccentrically within or on bone
  - Intramedullary tumors can produce erosion of cortex with component of tumor extending in soft tissues
  - Subperiosteal tumor may not involve medullary cavity
- Periphery of lesion usually delineated by shell of reactive bone, though this may not be visible on radiographs
  - Thickness of shell inversely related to rate of expansion

- Codman triangle may be present

### MR Findings

- Multiple cysts of varying size and may demonstrate internal soft tissue septa and characteristic fluid-fluid levels
  - Internal septation delineating cysts
  - Cysts have variable signal intensity with surrounding low T1 and T2 signals
    - Fluid-fluid levels prominent
      - Caused by settling of red blood cells displacing serum to surface, and different mass densities are manifested on sequences
      - Patient must be motionless for at least 10 minutes for red blood cells to settle
- Exhibit only modest levels of enhancement; septa may be prominent
- Edema of adjacent marrow and neighboring soft tissues
- Optimal to detect solid component

### CT Findings

- Lytic tumor with well-delineated margins
- Multiloculated with fluid-fluid levels
- Periosteal shell of reactive bone
- Helps define anatomic extent of tumor

### Bone Scan

- Avid uptake on bone scan

## MACROSCOPIC

### General Features

- Large hemorrhagic sponge-like cystic mass that is well circumscribed
  - Variable size; usually larger than 5 cm
  - Soft tissue component surrounded by thin shell of firm white bone
- Multiple blood-filled cystic spaces separated by thin, tan-white septa
  - Septa may feel gritty
- More solid tan-white areas often present
  - Either represents solid portion of ABC wall or portion of primary tumor that developed secondary ABC-like change
  - Solid areas within ABC should be thoroughly sampled to identify presence of possible underlying primary neoplasm

## MICROSCOPIC

### Histologic Features

- Cyst wall composed of uniform plump spindle fibroblast-like cells that may be mitotically active
- Scattered multinucleated osteoclast-like giant cells
- Reactive woven bone
  - Lined by osteoblasts and follows contours of fibrous septa of cyst walls
- ~ 1/3 of cases contain matrix known as blue bone
  - Consists of woven bone that is mineralized in irregular fashion
  - Infrequently seen in other types of bone tumors
- Necrosis uncommon unless there has been pathologic fracture
- Solid ABC lacks blood-filled cystic spaces and is composed of elements that compose cyst wall
  - May be hypercellular, mitotically active, and contain woven bone

## ANCILLARY TESTS

### Immunohistochemistry

- There are no specific immunohistochemical findings in ABC; p63 can stain some tumor cells
- Spindle fibroblast-like cells may express smooth muscle actin
- Osteoclasts stain with CD68

### Genetic Testing

- FISH using break-apart probe for *USP6* can detect rearrangement

## DIFFERENTIAL DIAGNOSIS

### Giant Cell Reparative Granuloma

- Giant cell reparative granuloma and solid component of ABC are histologically very similar
  - Giant cell reparative granulomas typically arise in small bones and in jaw
- Usually solid mass without prominent cyst component
- Lacks t(16:17)

### Telangiectatic Osteosarcoma

- Can grossly simulate ABC
  - Fibrous septa in telangiectatic osteosarcoma contain overtly malignant neoplastic cells with marked pleomorphism and easily identifiable mitotic figures

### Secondary Aneurysmal Bone Cyst

- Variety of benign and malignant bone tumors can develop secondary ABC-like changes
  - Giant cell tumor, chondroblastoma, fibrous dysplasia, osteoblastoma, and osteosarcoma most common
- ABCs need to be carefully sampled histologically to exclude any underlying lesion, as tumor will behave as primary tumor
- Secondary ABC does not have cytogenetic abnormalities present in primary ABC

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2. Sukov WR et al: Frequency of USP6 rearrangements in myositis ossificans, brown tumor, and cherubism: molecular cytogenetic evidence that a subset of "myositis ossificans-like lesions" are the early phases in the formation of soft-tissue aneurysmal bone cyst. Skeletal Radiol. 37(4):321-7, 2008
3. Oliveira AM et al: Aneurysmal bone cyst variant translocations upregulate USP6 transcription by promoter swapping with the ZNF9, COL1A1, TRAP150, and OMD genes. Oncogene. 24(21):3419-26, 2005
4. Vergel De Dios AM et al: Aneurysmal bone cyst. A clinicopathologic study of 238 cases. Cancer. 69(12):2921-31, 1992

### Eccentric Lytic Tumor

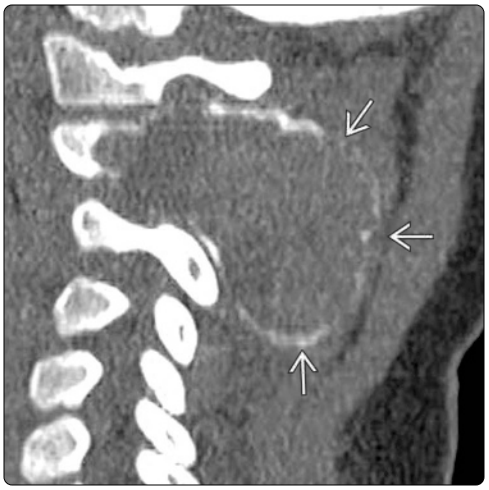


### Confined by Thin Periosteal Shell of Bone



**(Left)** *AP radiograph of the knee in a skeletally immature child shows a lytic lesion of the proximal tibial metaphysis extending to the growth plate. The bone margin appears relatively well demarcated and slightly sclerotic. The soft tissue margin is difficult to identify.* **(Right)** *Axial CT scan through an ABC shows that it has eroded the cortex and is demarcated from the soft tissues by partially mineralized periosteal new bone. The tumor has mixed signal intensity.*

### Expansile Mass



### Mass of Posterior Elements

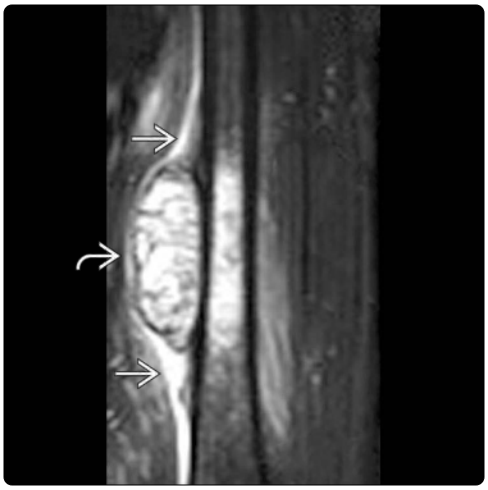


**(Left)** *Sagittal reformatted CT scan shows a very large and lytic ABC arising from the posterior elements of C2. The lesion is surrounded by a shell of periosteal bone and extends into the adjacent paraspinal muscles.* **(Right)** *Sagittal T2-weighted MR of a large ABC arising from the posterior elements of C2 shows multiple cyst chambers, some with characteristic fluid-fluid levels, and demarcation by low-signal fibrous walls.*

### Surface Tumor



### Well-Circumscribed Surface Mass



**(Left)** *Lateral radiograph of ABC arising in the mid tibial diaphysis shows a cortically based lesion with extension into the soft tissues. The tumor is well demarcated from the underlying bone and is surrounded by a very thin shell of periosteal new bone formation.* **(Right)** *Coronal T2-weighted MR shows a subperiosteal ABC. The periosteum is intact, but reactive periosteal bone formation is visible as a bright signal proximally and distally to the lesion. The adjacent medullary cavity is edematous.*

### Sharply Marginated Lytic Tumor



### MR With Fluid-Fluid Levels

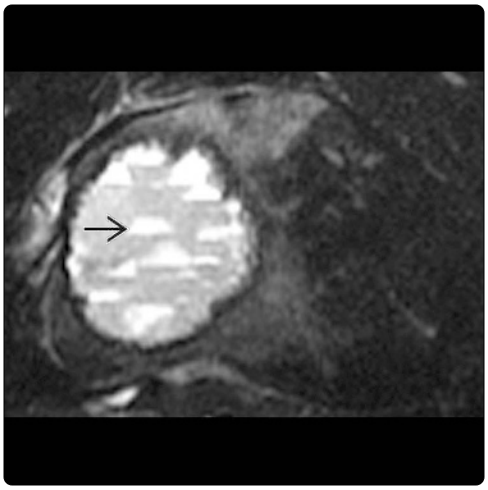


**(Left)** *A coronal reformatted CT scan shows an ABC that has a sclerotic sharp bony margin and has eroded the posterior cortex and extends into the soft tissues.* **(Right)** *A T2-weighted MR of an ABC demonstrates a fluid-fluid level that extends across the entire width of the lesion, indicating that there is no solid component. Fluids are best visualized on MR. This may be due to better soft tissue contrast afforded by MR or the fact that an MR examination takes longer to perform, facilitating settling of the cyst contents.*

### Eccentric Cystic Tumor

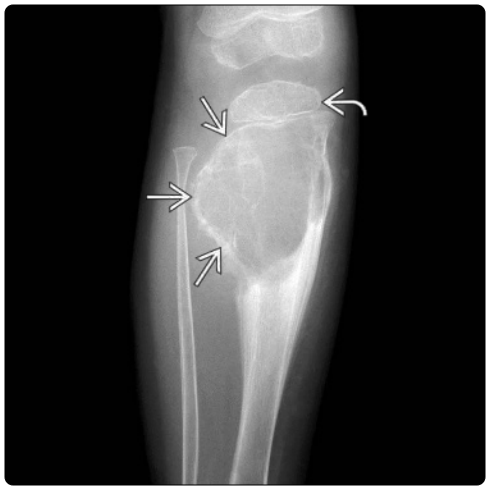


### Prominent Fluid-Fluid Levels

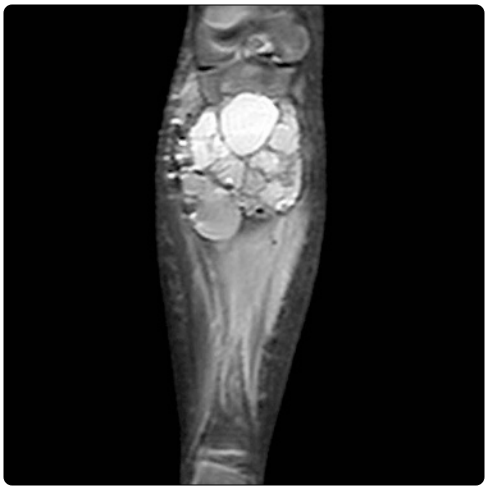


**(Left)** *Reformatted CT scan of an ABC of the tibia shows an eccentric lytic lesion that has a well-formed margin and a thin shell of periosteal bone. Fluid components are identified as low-attenuation areas, but fluid levels are absent. The patient was supine for this examination, and coronal reformations do not demonstrate fluid levels.* **(Right)** *Axial T2-weighted MR of an ABC of the tibia shows multiple fluid levels. The tumor is well circumscribed and scallops the underlying cortex.*

### Large Lytic Tumor



### Multiple Fluid-Filled Cysts

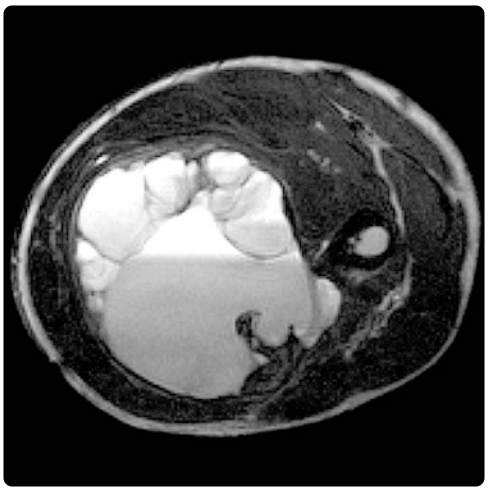


**(Left)** *Radiograph of a tibia in a child shows a lytic lesion extending to the open growth plate and into posterior soft tissues. The lesion is surrounded by a periosteal shell of bone.* **(Right)** *Coronal T2-weighted MR shows an ABC. Some of the cystic regions appear bright due to fluid contents, while others are dark due to cellular material in dependent position. Fluid levels are not visible on coronal images since, with the patient in a supine position, the levels are in same plane as scans.*

### Destructive Mass

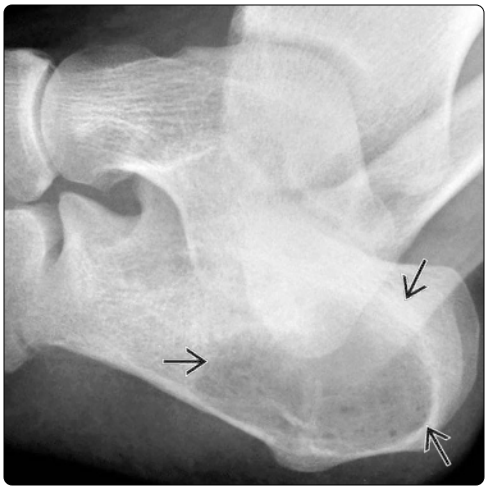


### Large Cysts



**(Left)** *Lateral radiograph of an ABC of the forearm shows a trabeculated lesion arising in the diaphysis of the ulna. The tumor has destroyed the cortex and extends into adjacent soft tissues where it is surrounded by a shell of periosteal bone formation* ⇨. **(Right)** *Axial T2-weighted MR of a very large ABC of the ulna shows multiple cystic cavities with the characteristic fluid-fluid levels. The tumor has destroyed the bone and extended into adjacent soft tissues.*

### Lytic, Well-Circumscribed Tumor

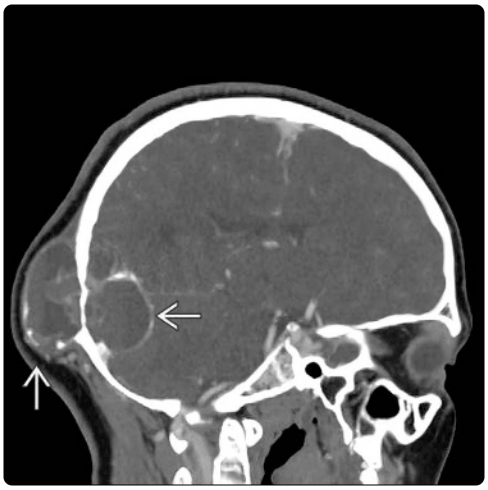


### Well-Defined Tumor



**(Left)** *A lytic ABC of the calcaneus* ⇨ *is seen in a skeletally mature individual. Although the lesion is relatively well demarcated with a sclerotic rim, suggesting that it might be noninvasive, there are no features that would enable a definite diagnosis of ABC based on this radiograph.* **(Right)** *T1-weighted, contrast-enhanced, fat-suppressed MR of an ABC shows that the lesion is composed of multiple nonvascularized spaces surrounded by enhancing walls characteristic of ABC.*

### Large ABC of Skull

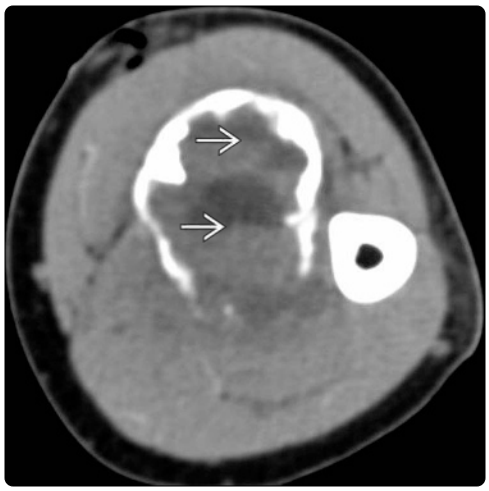


### Tumor Compresses Brain



**(Left)** *Sagittal CT shows a very unusual ABC of the skull with an intracranial and extracranial component. The cystic components are represented by areas of low attenuation, which are surrounded by a thin shell of bone* ⇨. **(Right)** *Axial CT scan shows that, in this instance, the fluid-fluid levels are clearly demonstrated. On CT, the pure fluid appears dark due to low x-ray attenuation, unlike on a T2-weighted MR where it appears bright due to high water content.*

### Expansile Tumor With Cortical Erosion

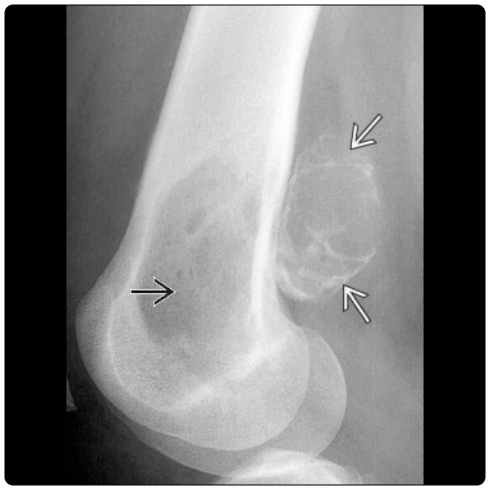


### Prominent Fluid-Fluid Levels

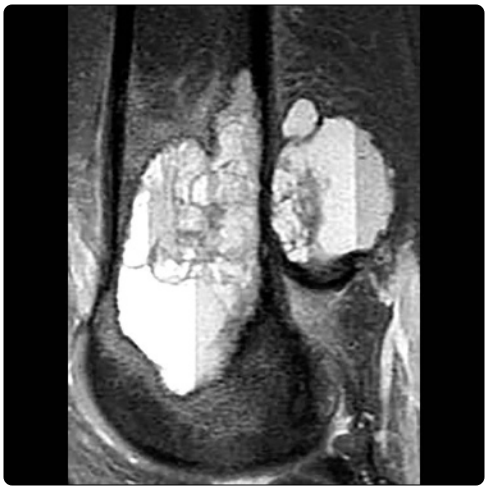


**(Left)** *Axial CT of an ABC of the tibia is shown. The tumor fills the medullary cavity and has eroded the cortex and expanded the bone. Subtle fluid-fluid levels are present within the cysts. The peripheral portion is surrounded by reactive bone.* **(Right)** *Axial T2 fat-saturated MR of the posterior tibia shows that the tumor is eccentric in location. The tumor is sharply marginated from the adjacent medullary cavity. Fluid-fluid levels are prominent.*

### Large ABC Growing Into Soft Tissues



### Soft Tissue Extension

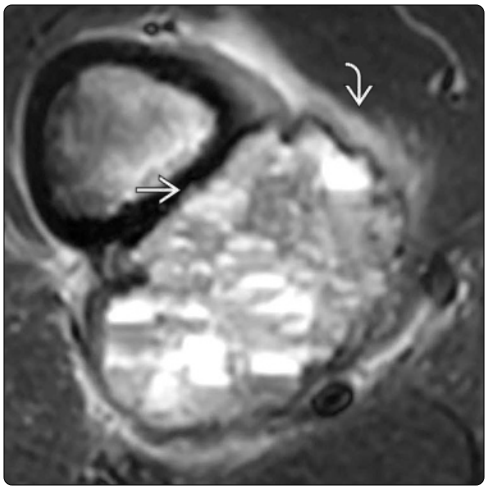


**(Left)** *Lateral radiograph of a large ABC shows that the tumor is lytic and is centered in the metaphyseal-diaphyseal region of the distal femur. The tumor extends through the posterior cortex into the soft tissues. Reactive bone surrounds the soft tissue component.* **(Right)** *Sagittal proton density fat-saturated image of a large ABC that is present in the medullary cavity and has extended into the posterior soft tissues is shown. The tumor is well circumscribed and has prominent fluid-fluid levels.*

### Eggshell-Like Mass on Surface of Femur



### Blister on Bone

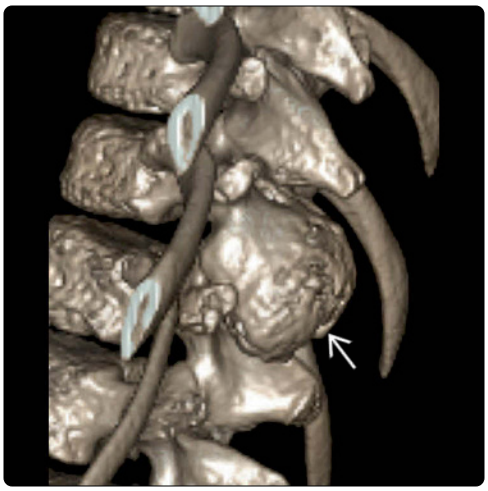


**(Left)** *A large ABC is subperiosteal and arises from the surface of the femur. The mass is subtle and delineated by a thin eggshell-like layer of mineralized bone. The medullary cavity is not involved. A Codman triangle is present proximally.* **(Right)** *Axial stir MR shows an ABC that is subperiosteal in location. The tumor is well circumscribed and is composed of multiple cysts that have fluid-fluid levels. The cortex is corrugated by the tumor. The adjacent soft tissues show a rim of increased signal that represents edema.*

**Balloon-Like Expansion**



**Bulbous Mass**



**(Left)** *Sagittal CT demonstrates an ABC of the posterior elements of the thoracic spine. The tumor is delineated by a thin shell-like rim of mineralized reactive bone. Fluid-fluid levels are not apparent.* **(Right)** *In this 3D reformatted CT, an ABC expands the posterior elements of the spine forming a bulbous mass. The tumor is well circumscribed from the adjacent soft tissues.*

**Lytic Expansile Tumor**



**ABC of Phalanx**

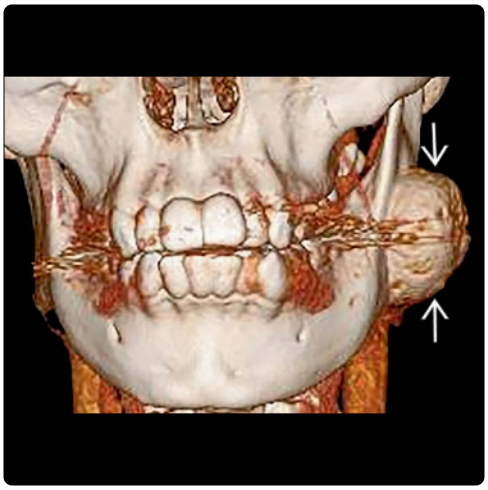


**(Left)** *Lateral radiograph of an ABC of the hand in a child shows a lytic lesion arising within, and greatly expanding, the proximal phalanx of the 4th digit. The lesion extends to the distal open growth plate and is surrounded by intact and ossified periosteum.* **(Right)** *Sagittal T2-weighted MR shows an ABC of the proximal phalanx. The tumor involves the diaphysis and metaphysis and exhibits the characteristic fluid-fluid levels.*

**Subperiosteal Mass On Mandible**

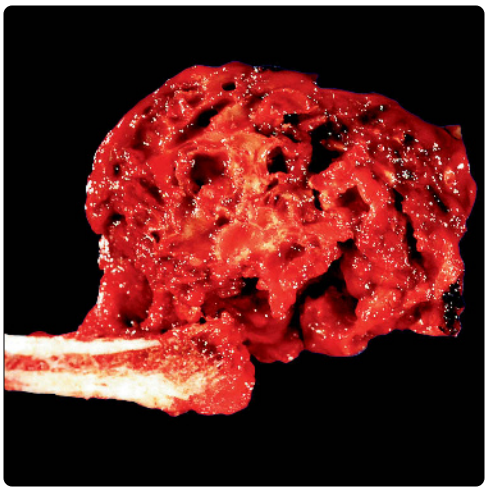


**Palpable Mass**

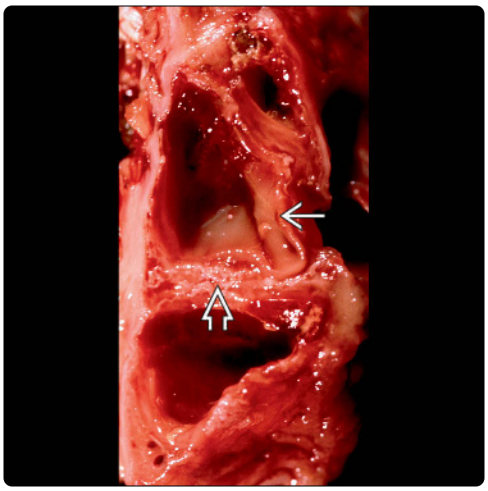


**(Left)** *Subperiosteal ABC is present on the surface of the external surface of the mandible. The periphery of the tumor is surrounded by a rim of subperiosteal reactive bone. A solid component is present in the inferior 1/2 of the mass.* **(Right)** *In this 3D reformatted CT, the subperiosteal ABC is present on the surface of the mandible. The tumor produces a palpable mass that can cause a cosmetic deformity.*

**Large Extraosseous Component**

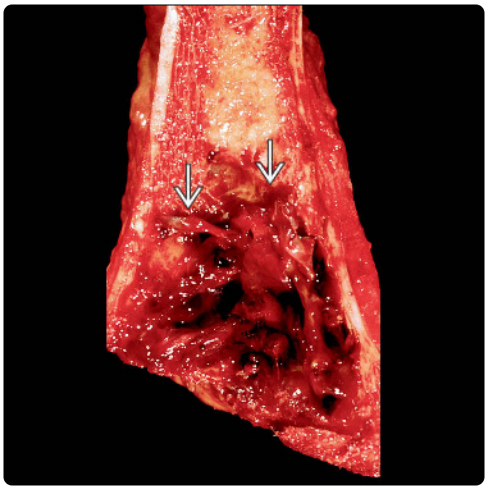


**Cystic Spaces**

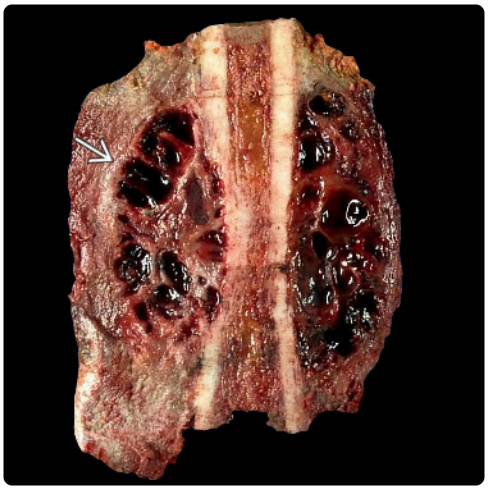


**(Left)** *A large subperiosteal ABC of the clavicle forms a large extraosseous soft tissue mass. The tumor is composed of blood-filled cystic spaces delineated by thick fibrous septa.* **(Right)** *An ABC arising in the posterior elements of the spine consists of several large cystic spaces; the blood has been washed from the lumina. The tumor is surrounded by a rim of reactive subperiosteal bone ➡, which also courses through the septa ➡.*

**Hemorrhagic Cysts**

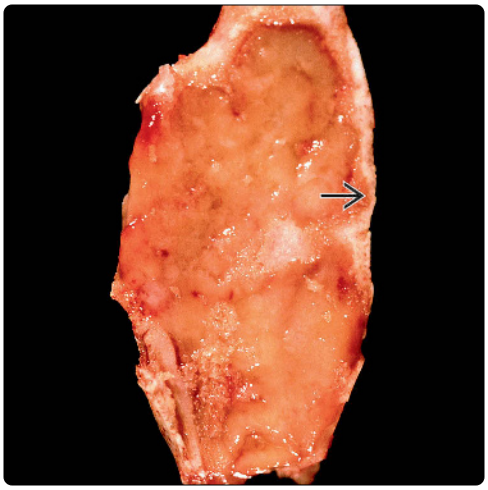


**Hemorrhagic Cystic Surface Mass**

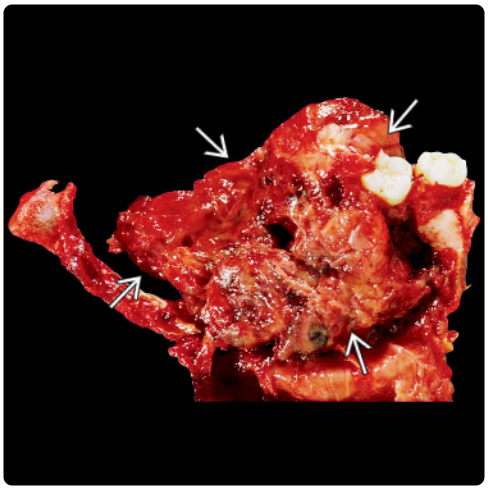


**(Left)** *An ABC arising in the medullary cavity of the distal femur contains numerous hemorrhagic cysts delineated by septa. The tumor does not expand the bone and has a sharp margin proximally ➡.* **(Right)** *A large subperiosteal ABC is seen arising on the surface of the femur without intramedullary involvement. The cystic and hemorrhagic tumor erodes the outer cortex and is delineated from the adjacent muscle by a rim of subperiosteal reactive bone ➡.*

**Solid ABC**

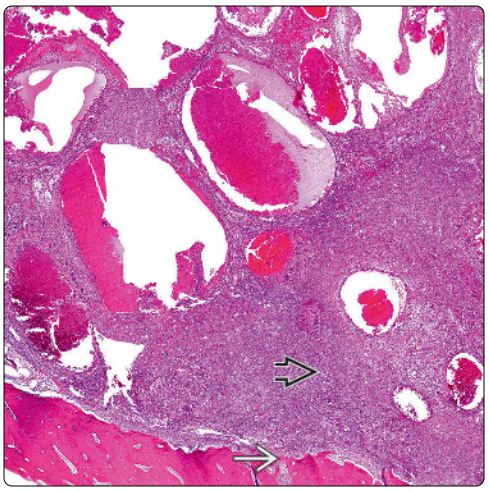


**Tumor Expanding Mandible**

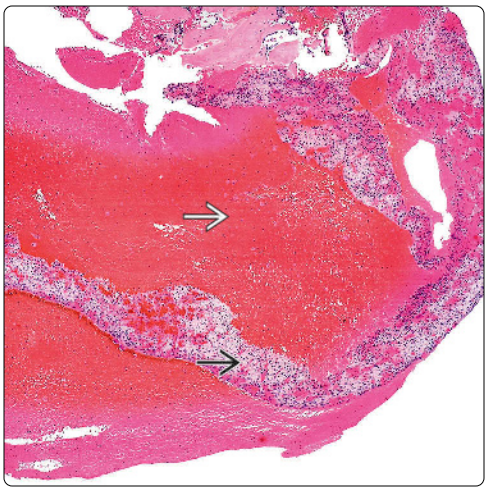


**(Left)** *This solid ABC arose in and expanded the rib. The tumor is homogeneous and tan-yellow without any blood-filled cystic cavities. The endosteal surface is scalloped by the mass ➡.* **(Right)** *Resected ramus of the mandible contains an ABC ➡ that expands the bone adjacent to several teeth. The peripheral cyst wall is friable and hemorrhagic.*

Multiple Blood-Filled Cystic Spaces

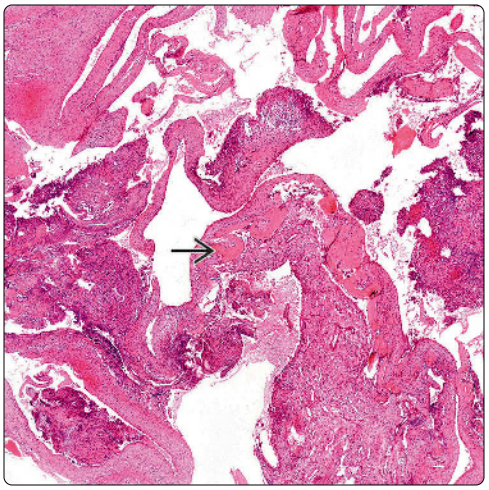


Blood-Filled Cystic Spaces

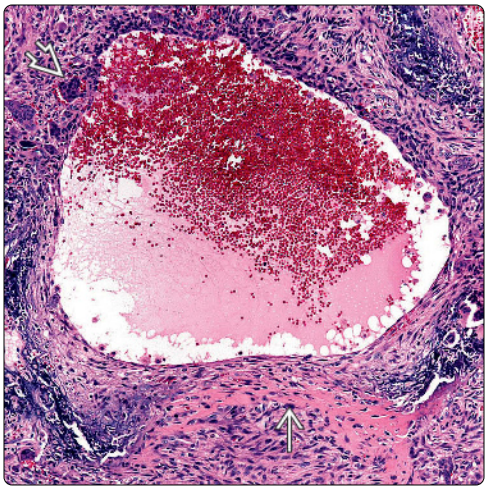


**(Left)** *A low-power view of an ABC shows a cellular neoplasm with multiple blood-filled cystic spaces. The tumor is arising in the medullary cavity of the bone and scallops the inner surface of the cortex. Note the solid portion of the tumor.* **(Right)** *A curettage specimen of an ABC arising in the tibia consists of blood-filled cystic spaces and portions of a cellular cyst wall.*

Fragments of Cyst Wall

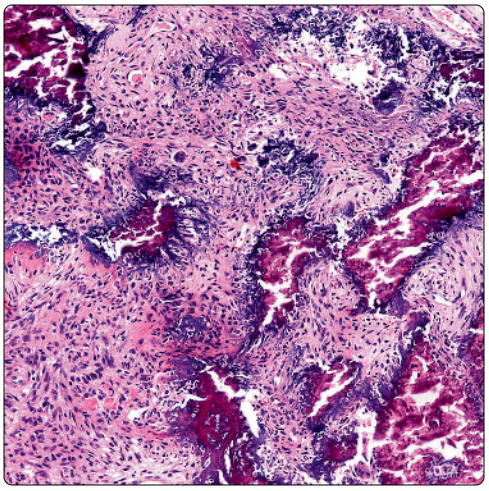


Blue Bone Formation

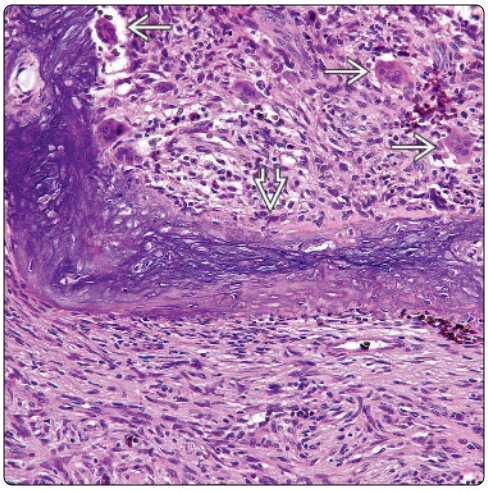


**(Left)** *A curettage specimen of an ABC is composed of a fragmented cyst wall that is of variable thickness. The cyst wall is cellular, and portions contain reactive woven bone that is deposited parallel to the contour of the wall.* **(Right)** *A blood-filled cystic cavity in an ABC is surrounded by a cellular wall composed of spindle-shaped cells, osteoclast-type giant cells, and reactive woven bone that in areas has the blue bone appearance and is focally rimmed by osteoblasts.*

Blue Bone

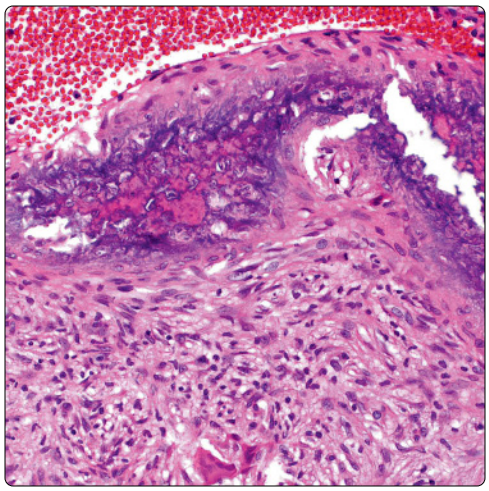


Prominent Blue Bone

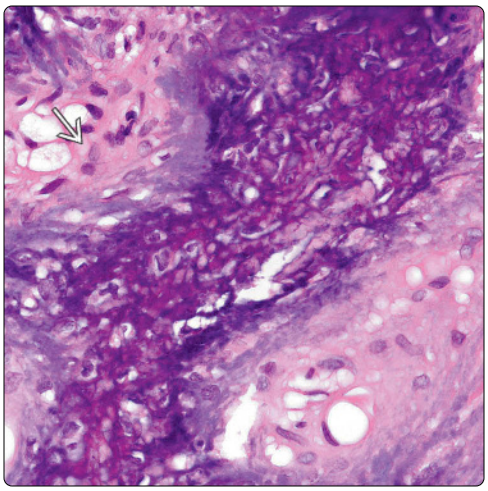


**(Left)** *The wall of an ABC is cellular with prominent reactive woven bone formation. A large portion of the bone is blue in color. This so-called blue bone is frequently seen in ABCs, although it is not diagnostic.* **(Right)** *The wall of an ABC displays reactive woven bone that is blue-purple in color (so-called blue bone). The bone has osteoblastic rimming, and the wall contains bland, spindle-shaped cells and scattered osteoclast-type giant cells.*

**Cyst Wall With Blue Bone**

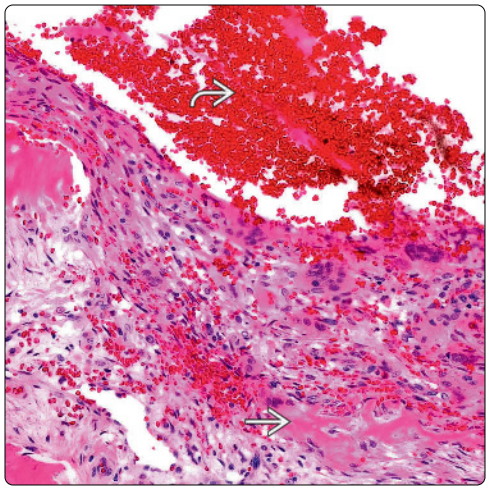


**Blue Bone**

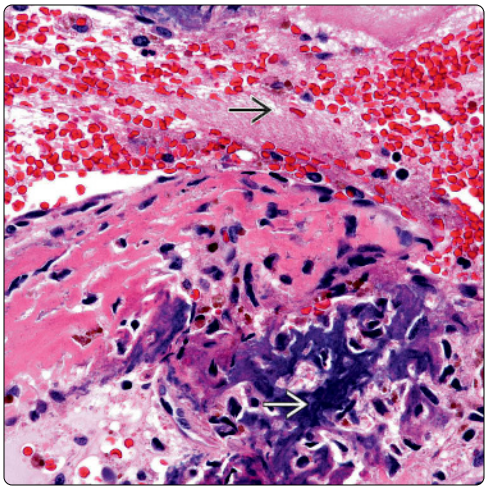


**(Left)** *The thick cyst wall of ABC contains an admixture of spindle cells, osteoclast-like giant cells, and reactive woven bone. The bone follows the contour of the cyst wall and is composed of coarse woven bone that is blue-purple in color when mineralized.* **(Right)** *The blue bone characteristic of ABC is composed of mineralized coarse woven bone. The surfaces are usually lined by a subtle layer of osteoblasts.*

**Wall of ABC**

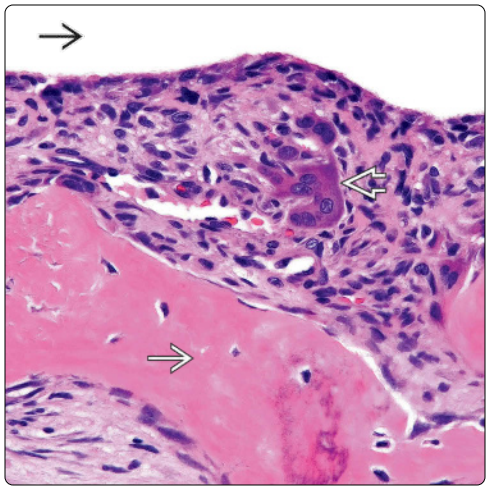


**Irregular Blue bone**

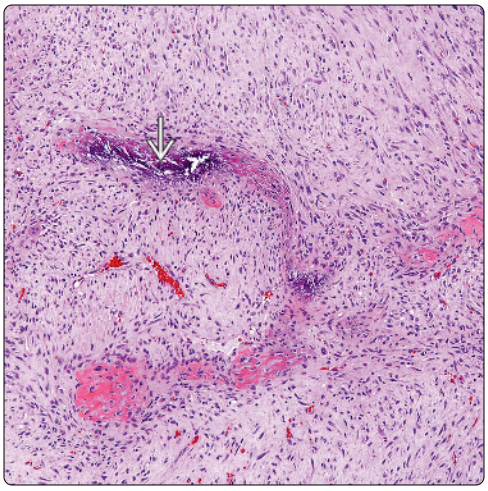


**(Left)** *This ABC shows a cystic cavity filled with red blood cells and surrounded by a wall composed of spindle-shaped cells, scattered osteoclast-type giant cells, and focal reactive bone with osteoblastic rimming.* **(Right)** *High-power view of an ABC shows hemorrhage and fibrin within the cyst cavity and a cyst wall containing woven bone, which is partially blue in color.*

**Wall With Reactive Woven Bone**

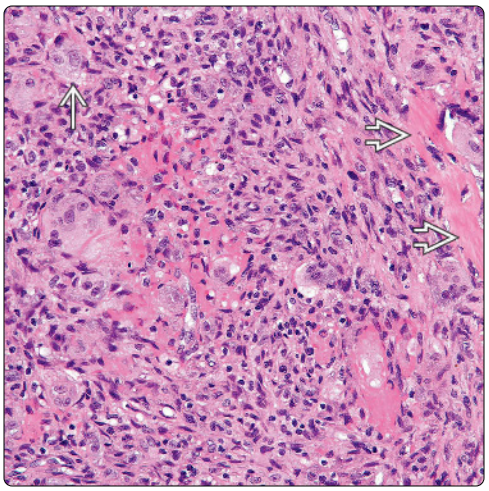


**Solid Variant of ABC**

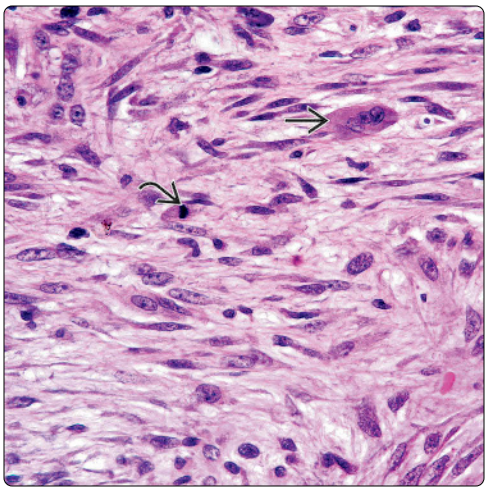


**(Left)** *High-power view shows the wall from an ABC that lacks a distinct cell lining of the cystic cavity. The cyst wall is cellular and composed of bland spindle cells with scattered osteoclast-type giant cells and reactive woven bone with osteoblastic rimming.* **(Right)** *A solid variant of an ABC is typically cellular and composed of spindle-shaped cells and contains a reactive bone formation that is focally pink-purple in color.*

Solid ABC

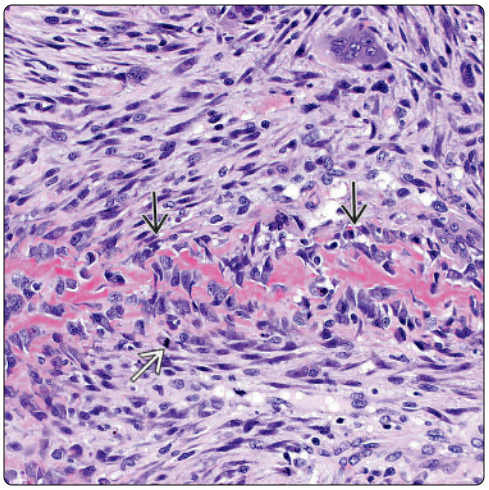


Proliferating Spindle Cells

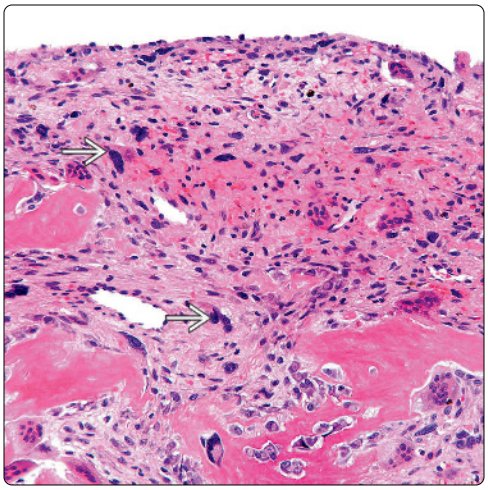


**(Left)** *A solid variant of an ABC has the same histologic features as the cyst wall of a conventional ABC being composed of cytologically bland, spindle-shaped cells, osteoclast-type giant cells, and reactive woven bone formation with osteoblastic rimming.* **(Right)** *A solid variant of an ABC is composed of mitotically active, cytologically bland, spindle-shaped cells with eosinophilic cytoplasm resembling myofibroblasts and scattered osteoclast-type giant cells.*

Mitotic Activity

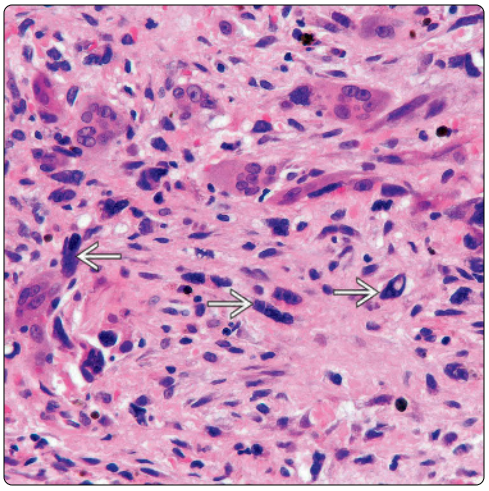


Pseudomalignant ABC

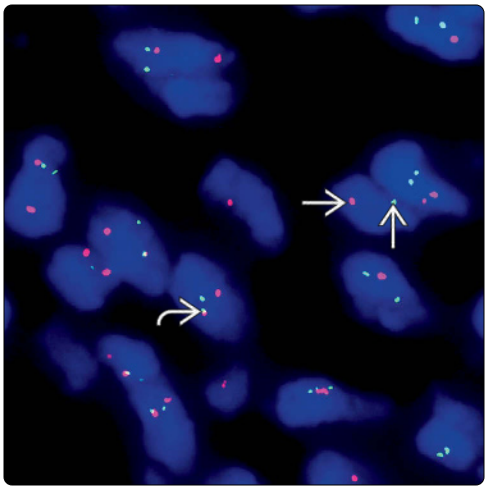


**(Left)** *The wall of ABC can be hypercellular & composed of fascicles of spindle cells. The spindle cells have plump, elongate nuclei & have fine chromatin. The cells may be mitotically active; however, the mitoses are of normal structure. The combination of hypercellularity & woven bone can cause confusion with osteosarcoma.* **(Right)** *A pseudomalignant ABC demonstrates large hyperchromatic cells throughout cyst wall. The cells appear degenerative in nature & lack mitotic activity.*

Pseudomalignant ABC



FISH for *USP6*



**(Left)** *ABC has pseudomalignant change with numerous large, hyperchromatic nuclei among bland, spindle-shaped cells and osteoclast-type giant cells. The atypia is manifested by intranuclear vacuoles and smudging, and these cells do not show mitotic activity.* **(Right)** *FISH using a break-apart probe shows rearrangement of the USP6 gene on chromosome 17p13 demonstrated by the separation of the green and red signals. The yellow signal represents the normal USP6 locus.*

# Epidermoid Inclusion Cyst

KEY FACTS

## TERMINOLOGY

- Epidermoid inclusion cyst (EIC) involving bone
- EIC forms when squamous epithelium becomes embedded in bone, proliferates, and forms mass
- When adnexal structures are present in walls of cysts, they are called dermoid cysts or dermoids

## CLINICAL ISSUES

- Acrally located lesions usually in young to middle-aged individuals
- Usually occur in fingers and toes (acral skeleton)
- Skull is 2nd most common site and affect children in 1st decade of life
- Can be asymptomatic, cause swelling, pain, and tenderness, and rarely present with pathologic fracture

## IMAGING

- Lytic, well defined with sclerotic margins

## MACROSCOPIC

- Lesions filled with soft, cheesy material (keratinous debris)
- Acrally located lesions are small
- Lesions arising in skull range in size from few millimeters to many centimeters

## MICROSCOPIC

- Cyst wall lined by benign squamous epithelium similar to epithelial inclusion cysts of skin

## TOP DIFFERENTIAL DIAGNOSES

- Enchondroma
- Giant cell reparative granuloma
- Osteomyelitis
- Glomus tumor

## DIAGNOSTIC CHECKLIST

- Cyst composed of benign keratinizing squamous epithelium

**Epidermoid Cyst of Finger**

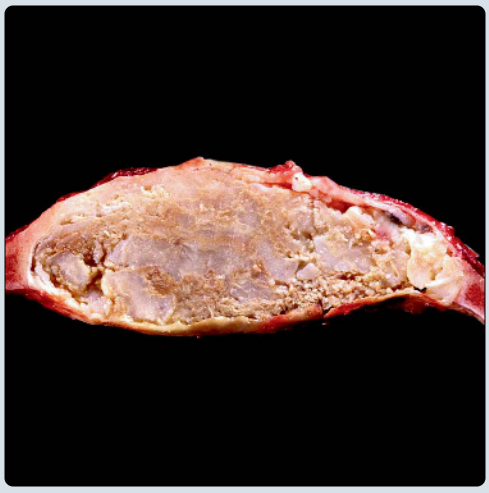


**MR of Epidermoid Cyst**

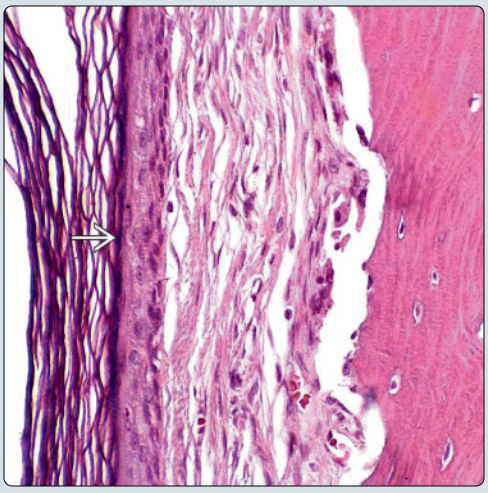


**(Left)** *AP radiograph of an epidermoid inclusion cyst of the distal digit is lytic, sharply marginated, and has caused expansion and thinning of the cortices. A small pathologic fracture is present.* **(Right)** *Coronal fluid-sensitive T2-weighted MR shows that this epidermoid inclusion cyst of the distal digit is confined to the bone and has a bright signal intensity.*

**Gross Photo of Epidermoid Cyst**



**Histology of Epidermoid Cyst**



**(Left)** *Epidermoid inclusion cyst of the skull has produced an expansile mass that has distorted the bone. The lesion is composed of friable, tan-gray-brown material and is sharply demarcated from the bone.* **(Right)** *The cyst wall is composed of keratinized squamous epithelium ⇨, which overlies fibrous tissue and abuts the bone.*

## TERMINOLOGY

### Abbreviations

- Epidermoid inclusion cyst (EIC)

### Definitions

- EIC is displaced squamous epithelium within bone, proliferates, produces abundant keratin, and forms mass
- When adnexal structures are present in walls of cysts, lesion is designated dermoid cyst

## ETIOLOGY/PATHOGENESIS

### Developmental Anomaly

- Some are thought to be due to trauma causing implantation of epidermis into bone
- Dermoid cysts are considered to be congenital in origin

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Very rare; incidence is unknown
- Age
  - Acrally located lesions usually arise in young to middle-aged individuals
  - Lesions of skull arise in children during 1st decade of life
- Sex
  - More common in males

### Site

- Epidermoid cysts usually occur in fingers and toes (acral skeleton)
  - Skull is 2nd most common location
- Most are solitary but infrequently multiple lesions may occur
- Dermoid cysts are restricted to skull

### Presentation

- May be asymptomatic
- Can present with swelling, pain, and tenderness
- Rarely present with pathologic fracture
- Skull lesions are usually asymptomatic or cause painless lump

### Treatment

- Simple curettage

### Prognosis

- Excellent
- Very rarely, squamous cell carcinoma can arise in EIC
  - Has only been reported in lesion affecting skull
    - These tumors behave in aggressive fashion
  - Squamous cell carcinoma has not been reported in EICs arising in small bones

## IMAGING

### Radiographic Findings

- Lytic
- Well defined
- Sclerotic margins
  - Sometimes ill defined, simulating infection
- Bone may be expanded

### MR Findings

- T1 hypointense
- T2 hyperintense

## MACROSCOPIC

### General Features

- Lesions filled with soft, cheesy material (keratinous debris)
  - Identical to EIC of skin
- Easily detached from adjacent bone
- Acrally located lesions are small
- Lesions arising in skull range in size from few millimeters to many centimeters

## MICROSCOPIC

### Histologic Features

- Cyst wall lined by benign keratinizing squamous epithelium and filled with keratin debris
  - Histologically identical to EIC of skin
  - Squamous epithelium has granular cell layer
- Ruptured cyst causes surrounding reactive process with histocytic and giant cell reaction
- In dermoid cysts, adnexal structures are present within walls of cyst

## DIFFERENTIAL DIAGNOSIS

### Enchondroma

- Radiographic differential diagnosis
- Can also cause lytic, well-defined lesion in bone
- Easily distinguished histologically as is composed of cartilage

### Giant Cell Reparative Granuloma

- Radiographic differential diagnosis
- Like EIC, may present as lytic lesion in small bones
- Does not contain squamous epithelium

### Osteomyelitis

- EICs can clinically mimic osteomyelitis when they present with swelling, pain, and tenderness

### Glomus Tumor

- Glomus tumor may appear identical to EIC radiographically

### Healing Eosinophilic Granuloma

- Can mimic EIC of skull radiographically

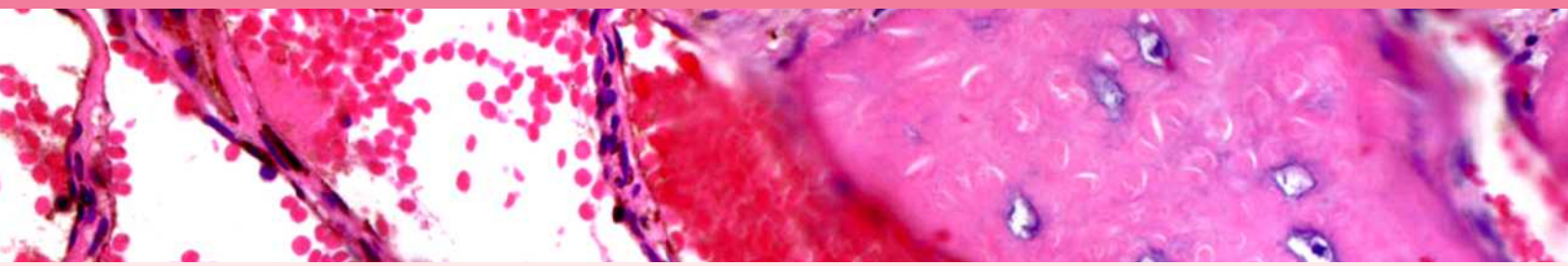
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SECTION 11

# Vascular Tumors




| | |
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| Epithelioid Hemangioma | **320** |
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| Epithelioid Hemangioendothelioma | **334** |
| Angiosarcoma | **340** |

# Conventional Hemangioma

KEY FACTS

## CLINICAL ISSUES

- Among most common primary benign tumors of bone
- Most commonly arise in vertebral bodies
- Clinically significant hemangiomas account for < 1% of primary bone tumors
- Incidental lesions require no treatment
- Gorham disease (disappearing bone disease, massive osteolysis) is variant of hemangioma/lymphangioma

## IMAGING

- Skull and long bones: Intralesional radiating spicules of bone give rise to internal web-like trabecular (starburst) pattern
- Tend to have coarse trabeculations due to rebuttressing of residual bony trabeculae that are encompassed by tumor (corduroy appearance)
- Fatty component of lesion is usually demonstrable by MR
- High-density round foci (corresponding to thickened vertical trabeculae) mixed with low-attenuation fat results in characteristic polka dot pattern in vertebral bodies

## MICROSCOPIC

- Usually of capillary or cavernous type
- Lumina are lined by single layer of flat, uniform, cytologically bland endothelial cells
- Gorham disease is variant of hemangioma

## TOP DIFFERENTIAL DIAGNOSES

- Epithelioid hemangioma
- Epithelioid hemangioendothelioma

## DIAGNOSTIC CHECKLIST

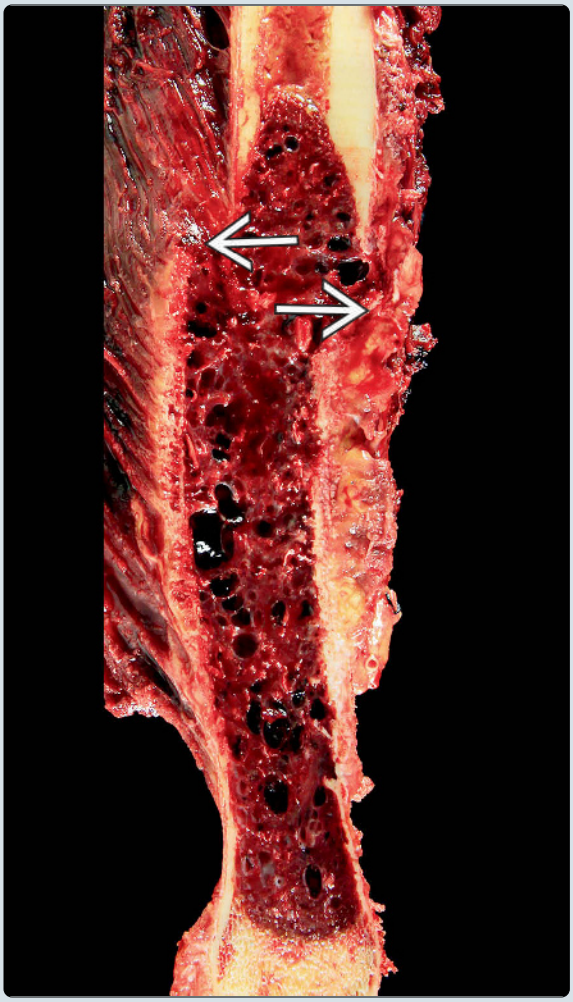
- Most hemangiomas grow with infiltrative pattern in medullary cavity
- Vessels are lined by benign-appearing endothelial cells
- Vascular walls may be difficult to appreciate in fragmented needle biopsy or curettage specimens

**Multiple Lucencies**



*This is an unusual example of a hemangioma of the femur. The tumor manifests as multiple oval radiolucencies that involve the medullary canal and cortex. The margins are sharp with no sclerosis.*

**Large Hemangioma**



*This hemangioma is remarkable for its large size. The tumor fills the medullary cavity of the distal half of the femoral diaphysis and has resulted in a displaced pathologic fracture ⇨. The red tumor has a spongy appearance and is sharply demarcated.*

## TERMINOLOGY

### Definitions

- Benign vascular neoplasm of bone showing endothelial differentiation

## ETIOLOGY/PATHOGENESIS

### Neoplastic

- Benign neoplastic proliferation of endothelial cells

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Among most common primary benign tumors of bone
    - ~ 10% of population has asymptomatic hemangiomas
      - Vast majority located in vertebral bodies
    - Clinically significant hemangiomas account for < 1% of primary bone tumors
- Age
  - Usually diagnosed in adulthood
    - Peak incidence: 5th decade
    - Tumors in children are often symptomatic
      - Wide distribution in skeleton
- Sex
  - F > M

### Site

- Most commonly arise in vertebral bodies
  - Distribution in spinal column
    - Thoracic vertebrae
    - Lumbar vertebrae
    - Cervical vertebrae
  - Symptoms develop when tumor compresses spinal cord or nerves or causes pathologic fracture
    - Compresses spinal cord or nerves by growing into spinal canal or expanding pedicles and lamina
- Also arise in craniofacial skeleton and long bones
  - Tumors of craniofacial skeleton often have sclerotic component
    - Sclerosis may be prominent on imaging studies
  - Metaphysis and diaphysis are often affected in long bones
- Multifocal disease has been categorized into 2 entities
  - Multiple primary hemangiomas of bone consist of collections of lesions that individually have radiographic findings and clinical behavior of solitary hemangiomas
  - Cystic angiomatosis present with diffuse, multifocal, lyric, skeletal tumors
    - Term cystic was based on their appearance on plain radiographs
    - May have visceral involvement

### Presentation

- Usually asymptomatic and incidental finding on imaging studies of spine
  - May produce pain or neurological symptoms
  - Often detected during work-up for another disorder
- Gorham disease (disappearing bone disease, massive osteolysis) is variant of hemangioma/lymphangioma
  - Rare disorder that is characterized by progressive dissolution of portion or all of 1 or several adjacent bones by contiguous growth
    - Dissolution of bone is caused by florid osteoclastic activity induced by neoplastic endothelial cells
    - Symptoms are variable and related to site of anatomic involvement
  - Lesion usually does not form solid or expansile mass
  - Tumor can cross joints
  - Can be fatal when important structural elements are affected
    - Skull base and cervical spine disease prone to severe complications
  - Affected bones are
    - Shoulder, skull, pelvic girdle, jaw, ribs, and spine
  - Can involve viscera
    - Such as lung

### Treatment

- Incidentally detected lesions require no treatment
- Symptomatic
  - Curettage and bone grafting
  - Cranial lesions
    - En block excision
  - Vertebral lesions
    - Transarterial embolization followed by decompression
- Radiation may be used in Gorham disease

### Prognosis

- Low rate of local recurrence
- Does not progress to angiosarcoma
  - Rare patients with multicentric disease have developed angiosarcoma in hemangioma after many years
- Patients with Gorham disease can have guarded outcome when skull base and spine are affected

## IMAGING

### Radiographic Findings

- Radiolucent due to relative loss of bone secondary to osteoclastic bone resorption and to presence of moderate to large quantities of fat within lesion
- Tend to have coarse trabeculations due to rebuttressing of residual bony trabeculae that are encompassed by tumor
  - Corduroy appearance
- Skull and long bones
  - Intralesional radiating spicules of bone give rise to internal web-like trabecular (starburst) pattern
- Gorham disease
  - Distinctive appearance on radiographs
    - Affected bones have region of complete lysis with residual ends being tapered and having appearance similar to licked candy stick

### MR Findings

- Fatty component of lesion is detected on MR
  - Important diagnostic hallmark because intralesional fat is not seen in malignant bone lesions
- Low signal intensity on T1-weighted images
  - Lesions with abundant fat show high signal on T1
- High signal intensity on T2-weighted images

### CT Findings

- Well-defined lytic lesions
- High-signal round foci (corresponding to thickened vertical trabeculae) mixed with low-attenuation fat results in characteristic polka dot pattern in vertebral bodies

## MACROSCOPIC

### General Features

- Resemble conventional hemangiomas of skin and soft tissue
- Usually centered in medullary cavity
- Dark red, sponge-like appearance
- May expand bone
- Bone sclerosis or periosteal reaction may be prominent

## MICROSCOPIC

### Histologic Features

- Usually of capillary or cavernous type
  - Vessel walls have thin walls
  - Vessels are usually round or oval in configuration and are branching
  - Vessels can grow with infiltrative pattern permeating medullary canal
  - Involved trabecular bone shows reactive sclerosis (bony rebuttressing)
- Lumina are lined by single layer of flat, uniform, cytologically bland endothelial cells
  - Lumina may not be filled with red blood cells
    - Lumina may be empty or contain amorphous proteinaceous material
- Vessels are surrounded by loose connective tissue
- Secondary changes, such as thrombosis, calcification, and papillary endothelial hyperplasia, may be seen
- Gorham disease
  - Reminiscent of capillary hemangioma or lymphangioma
  - Osteoclastic activity may be seen at leading edge
  - Vessels are not numerous enough to produce mass-like lesion
    - Their relatively few number can make diagnosis challenging
    - Correlation with imaging studies is very important

## ANCILLARY TESTS

### Immunohistochemistry

- Cells lining vascular channels uniformly stain for endothelial cell markers
  - Factor VIII-related antigen
  - CD31
  - CD34
  - ERG
  - FLI-1
  - Negative for keratin

### Genetic Testing

- *EWSR1-NFATC1* fusion has been described in one reported case

## DIFFERENTIAL DIAGNOSIS

### Epithelioid Hemangioma

- In epithelioid hemangioma, endothelial cells are large polyhedral epithelioid cells with densely eosinophilic cytoplasm
- Tumors may be multicentric in regional fashion, which is unusual for conventional hemangioma
- Tumor cells often have intracytoplasmic vacuoles
- Tumor cells can grow in solid sheets

### Epithelioid Hemangioendothelioma

- In epithelioid hemangioendothelioma, epithelioid endothelial cells are arranged in cords or clusters in myxohyaline stroma
- Vascular lumina are usually not present
- Intracytoplasmic vacuoles are prominent

### Angiosarcoma

- Neoplastic cells in angiosarcoma demonstrate greater degree of cytologic atypia
  - Nucleomegaly and hyperchromasia
- Tumor cells often grow in solid clusters
- Blood vessels have irregular configuration

### Reactive Process

- Blood vessels are fewer in number compared to most hemangiomas
- Blood vessels are not haphazardly arranged as in hemangioma
- Accompanying changes, such as reactive fibrosis, woven bone, and cartilage, often present

### Normal Structures

- Nutrient artery and vein and their branches
  - Branches can be clustered adjacent to one another
  - Can be associated with fibrous tissue and small amount of woven bone
  - Vessels have thick walls that are not seen in most hemangiomas
  - Vessels are arranged in lobular architecture

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Vascular walls may be difficult to appreciate in fragmented needle biopsy or curettage specimens
- Diagnosis of hemangioma should always be considered when confronted with bone biopsy that appears to be normal
- Consider hemangioma when bone contains many capillary-like vessels coursing through marrow space

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### Polka Dot Pattern

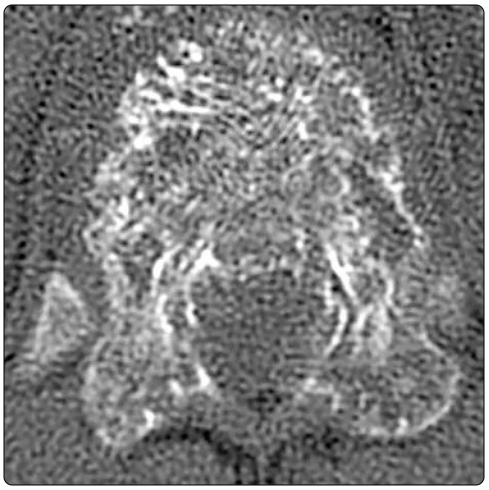


### Capillary Hemangioma



**(Left)** *Axial CT of a hemangioma involving a vertebral body shows low-attenuation tissue due to high fat content. Punctate high-density structures represent thickened trabeculae that extend through the lesion.* **(Right)** *Conventional intraosseous hemangioma arising in a vertebral body shows coarse trabeculation of the bone with a prominent fatty component. The lesion completely replaces the vertebral body.*

### Symptomatic Hemangioma of Spine

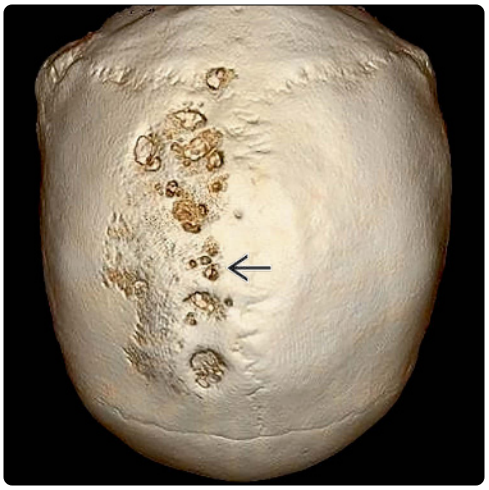


### Collapsed Vertebra



**(Left)** *The patient is 14 years old and has a large hemangioma that involves the vertebral body, pedicles, and lamina. The tumor appears as a lytic mass that is associated with prominent metaplastic bone. The vertebral body has collapsed, causing the symptoms.* **(Right)** *The large hemangioma of the vertebra has caused compression of the body. In this 3D reformatted image, the height of the affected vertebra is reduced and the anterior surface has an irregular surface caused by the fractured cortex.*

### Hemangioma Eroding Outer Table

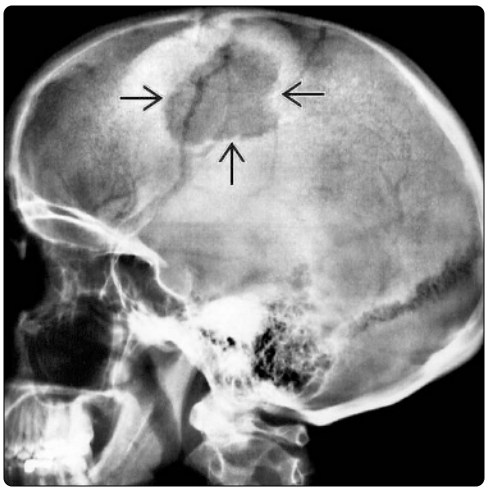


### Mass Protruding From Calvarium

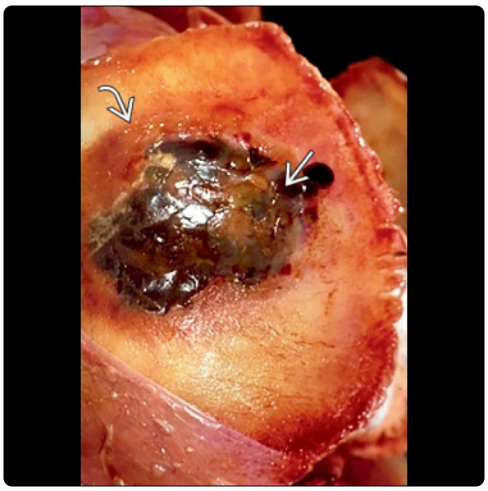


**(Left)** *Hemangioma often arises in the craniofacial bone. The tumor infiltrates the diploic spaces and can erode the inner and outer tables of the cranium. In this 3D reformatted CAT scan, the hemangioma has produced prominent erosions on the outer table.* **(Right)** *Hemangioma of the skull can expand the bone and present as a palpable mass. In this 3D reformatted CT, the tumor has eroded the outer table, forming a bulging tumor that is surrounded by a rim of reactive.*

**Lytic Tumor**



**Hemangioma of Calvarium**

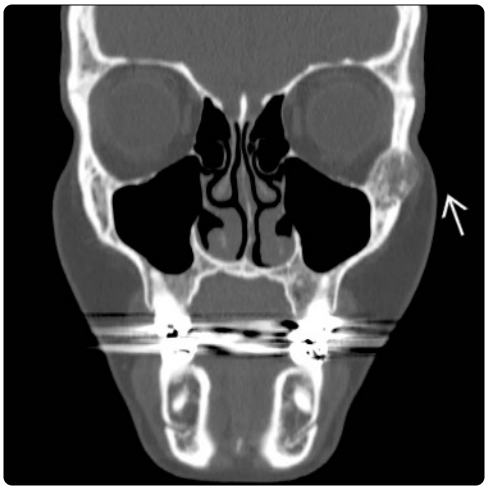


**(Left)** *Lateral skull radiograph of an intraosseous hemangioma demonstrates a large lytic lesion involving the parietal bone. Faint linear ossifications seen within the lesion, especially at its periphery, represent retained internal cancellous bone. There is a thick rind of sclerosis surrounding the lytic component.* **(Right)** *The hemangioma of the skull is dark red and has a nodular configuration. The tumor is surrounded by a rim of erythematous thickened bone that correlates with sclerosis on radiographs.*

**Hemangioma of Zygoma**



**Hemangioma of Zygoma**

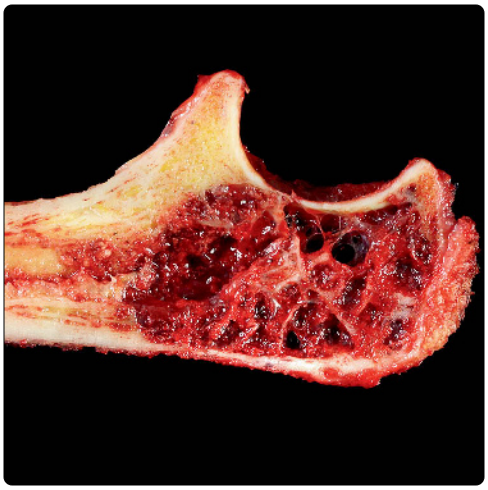


**(Left)** *Hemangiomas of the facial bones can cause cosmetic deformities. In this patient, the hemangioma involves the zygoma bone and causes its expansion.* **(Right)** *The zygoma is expanded by a hemangioma that has produced a cosmetic deformity, presenting as facial swelling and asymmetry. The hemangioma is well circumscribed with lytic and radiodense components.*

**Lytic Mass**



**Hemangioma of Olecranon**



**(Left)** *In this sagittal CT scan of the elbow, a large hemangioma can be seen involving the olecranon of the ulna. The tumor manifests as multiple round to oval hypointense areas sharply delineated from the surrounding bone.* **(Right)** *This hemangioma of the olecranon is composed of multiple bloody spaces that have thin walls and are spider-like in appearance. The overlying articular cartilage is unremarkable.*

### Hemangioma With Irregular Configuration

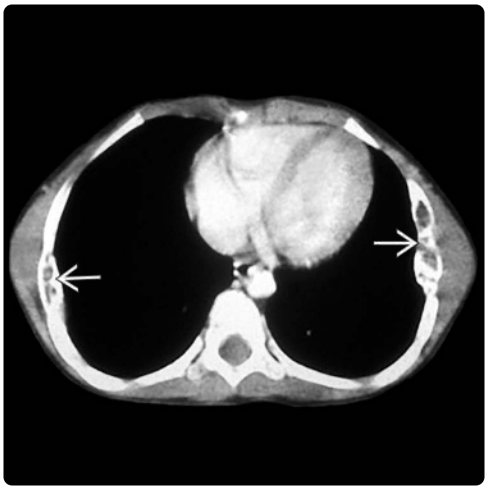


### Lobular Configuration

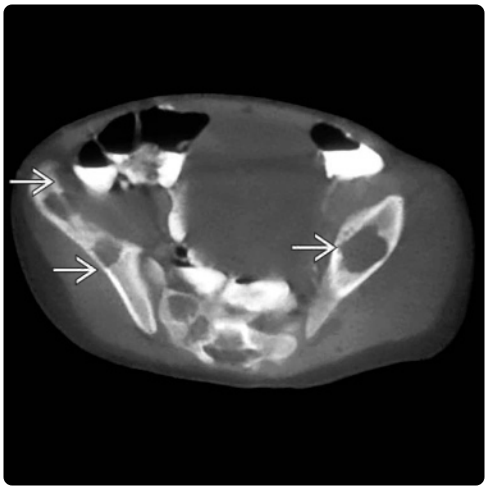


**(Left)** *The hemangioma in the distal femur has a multinodular appearance in this axial CT. The tumor has a low signal intensity* ➡ *and an irregular configuration. The tumor focally involves the cortex* ➡ *and has well-circumscribed margins.* **(Right)** *In this coronal PD of a hemangioma of the distal femoral metaphysis, the tumor has an increased signal intensity* ⇨ *and a lobular architecture. The surrounding dark rim represents a layer of reactive bone* ➡.

### Multiple Hemangiomas of Ribs



### Multiple Lytic Masses

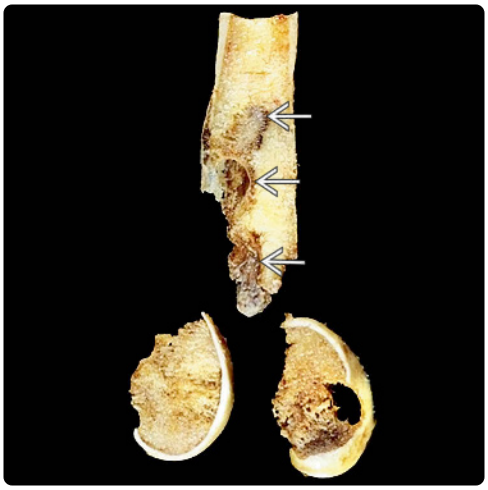


**(Left)** *Some hemangiomas are multifocal and have been designated cystic angiomatosis. The tumors are lytic, have expanded the ribs* ➡, *and have caused pathologic fractures. The tumors have transgressed the cortices and extend into the soft tissues.* **(Right)** *This patient has multiple hemangiomas of the skeleton. Axial CT shows large, oval, lytic tumors* ➡ *that have well-circumscribed margins.*

### Disappearing Bone



### Resorbed Portions of Femur



**(Left)** *This patient has a severe form of Gorham disease. The left portion of the pelvis and proximal femur have been resorbed by the disease* ➡. **(Right)** *This resected distal femur shows the features of Gorham disease. The lesion consists of small aggregates of neoplastic vessels that are red-brown in color* ➡ *resulting from the resorption of the distal diaphysis and metaphysis.*

**Graphic of Hemangioma**

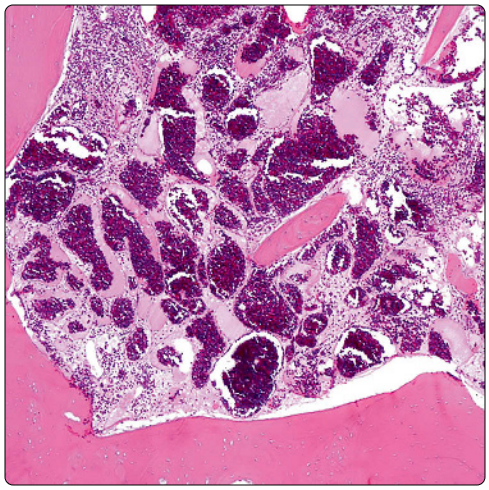


**Cavernous Vessels**

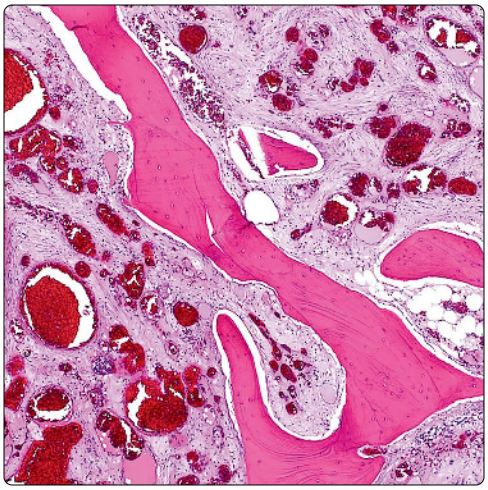


**(Left)** *Graphic shows how the hemangioma of the vertebra replaces the marrow and surrounds preexisting bony trabeculae.* **(Right)** *In this intraosseous conventional hemangioma, the tumor is composed of small, thin-walled vascular spaces* ⇨ *with attenuated endothelial lining, surrounded by a prominent fatty component. The tumor appears to be well demarcated and surrounded by bone.*

**Blood-Filled Vessels**

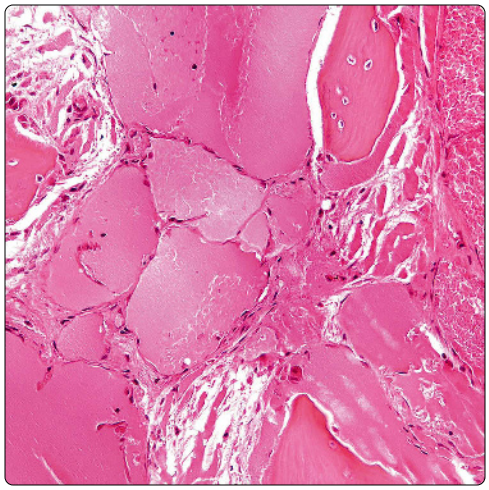


**Variably Sized Vessels**

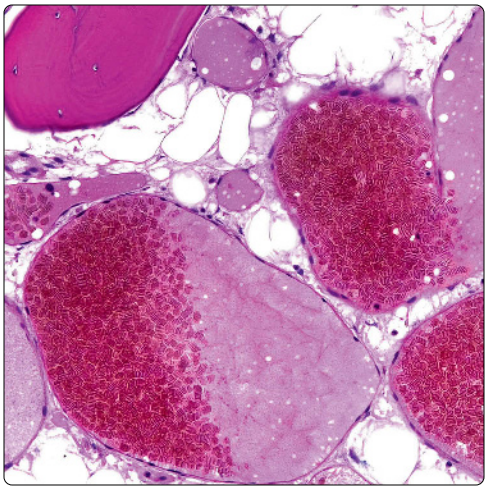


**(Left)** *Hemangioma of bone can be composed of cavernous, thin-walled, capillary-like spaces that are distended with blood, as in this case. Note how the vessels replace the marrow, and the preexisting bone is preserved.* **(Right)** *The medullary cavity of this bone contains a capillary hemangioma. The tumor is composed of well-formed, congested, capillary-like vessels that replace the marrow and surround the trabecular bone.*

**Cavernous Vessels**

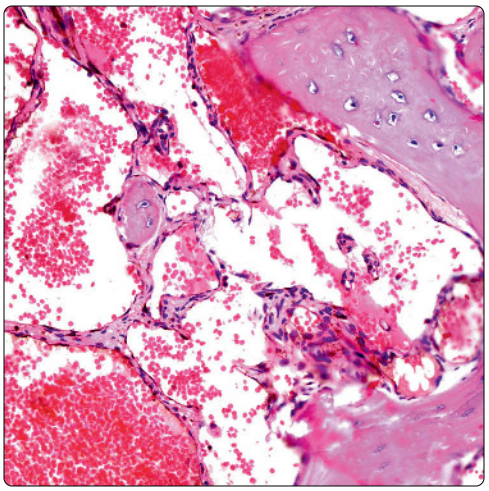


**Benign Endothelium**

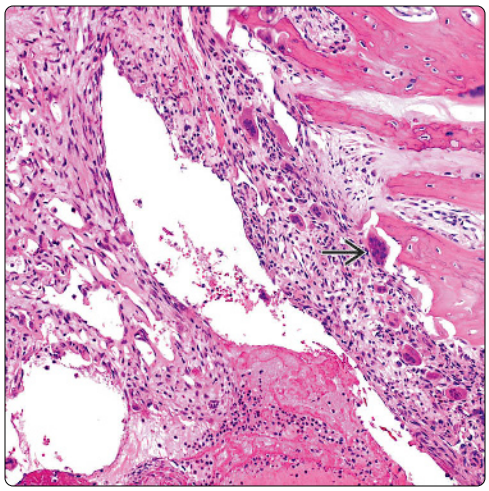


**(Left)** *Aggregate of dilated, blood-filled capillaries in a hemangioma is shown. The tumor is adjacent to the trabeculae of the lamellar bone.* **(Right)** *The endothelial cells lining the neoplastic vessels are spindle-shaped with banal-appearing nuclei.*

### Complex Interconnecting Pattern

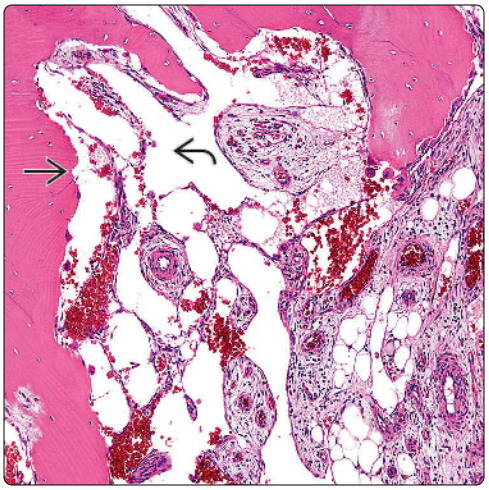


### Osteoclastic Activity

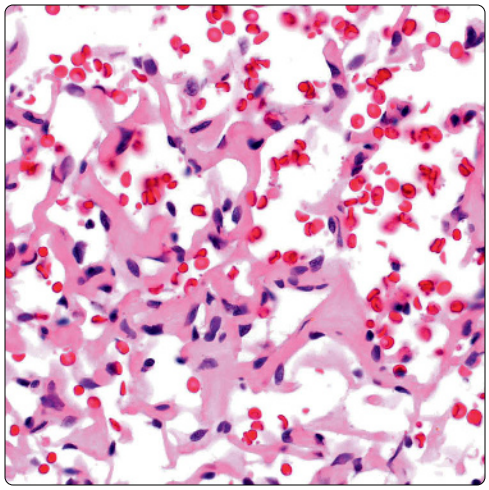


**(Left)** *High-power view of a conventional intraosseous hemangioma shows anastomosing vascular spaces with attenuated walls and flat endothelial cells. The surrounding bone is reactive and woven in nature.* **(Right)** *Sometimes, hemangiomas of bone produce lytic lesions on radiographs. This results from osteoclastic resorption of the involved portions of bone. In this case, a group of osteoclasts are digesting bone along the margin of the hemangioma.*

### Blood Vessels Causing Bone Resorption

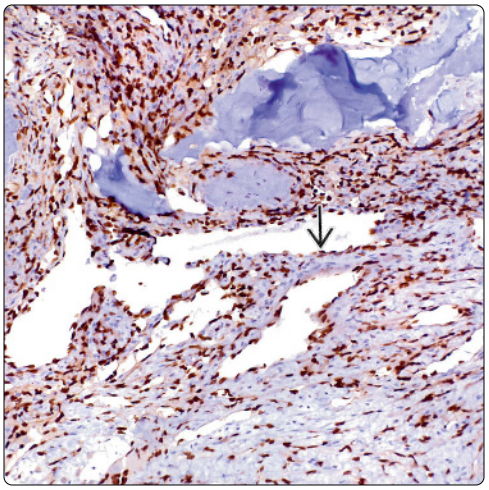


### Sieve Pattern

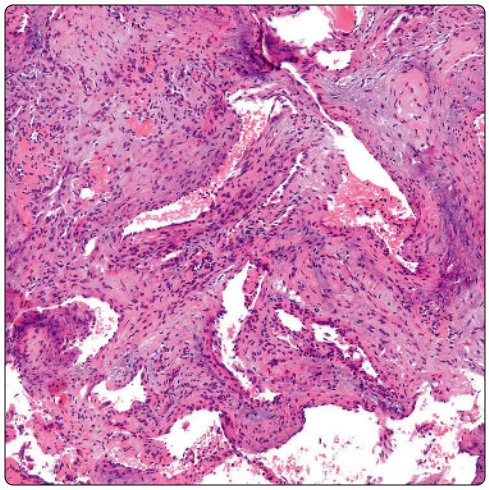


**(Left)** *This case of Gorham disease is composed of numerous vascular spaces lined by attenuated endothelium. The adjacent bone is scalloped, indicative of osteoclastic activity and explaining the lytic and aggressive nature of Gorham disease.* **(Right)** *The neoplastic cells in this hemangioma form a complex interconnecting network, which can mimic angiosarcoma. Some of the endothelial cells have plump nuclei.*

### Cellular Hemangioma



### Thick-Walled Vessels



**(Left)** *Immunohistochemistry using ERG antibodies highlights the nuclei of the neoplastic endothelial cells.* **(Right)** *This intraosseous conventional hemangioma of bone is composed of thick-walled, muscular, venous-like, blood vessels. The vascular lumina contain red blood cells, and the endothelial lining is flat and does not demonstrate any cytologic atypia.*

# Lymphangioma/Lymphangiomatosis

KEY FACTS

## TERMINOLOGY

- Primary bone tumor composed of lymphatic vessels

## CLINICAL ISSUES

- Very rare primary tumor of bone
- Can involve single bone (lymphangioma) or multiple bones (lymphangiomatosis) and soft tissue
- Symptoms depend on extent of disease
- No treatment needed for asymptomatic patients
- Very good prognosis when involving single bone
- Prognosis for lymphangiomatosis depends on extent of extraosseous involvement
- Symptomatic osseous lesion treated with curettage and packing

## IMAGING

- Well-circumscribed radiolucency

## MICROSCOPIC

- Vessels with irregular configuration
- Thin-walled spaces lined by flat endothelial cells
- Vascular lumina filled with proteinaceous fluid

## ANCILLARY TESTS

- Endothelial cells may stain with D2-40, CD3, and CD34

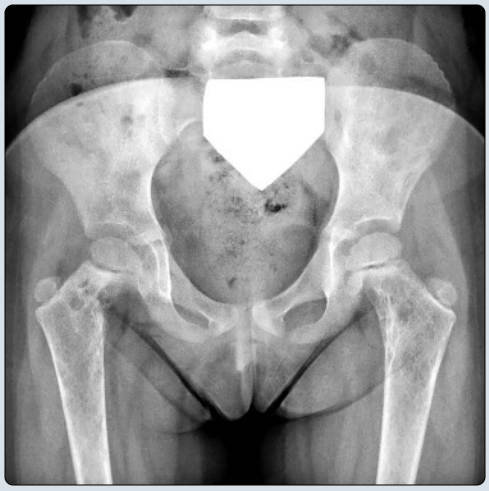
## TOP DIFFERENTIAL DIAGNOSES

- Hemangioma of bone
- Multifocal eosinophilic granuloma
- Enchondromatosis
- Metastatic carcinoma
- Polyostotic fibrous dysplasia

## DIAGNOSTIC CHECKLIST

- Possibility of vascular lesion should always be considered when encountering "normal bone" in biopsy specimen

**Multiple Lytic Tumors**

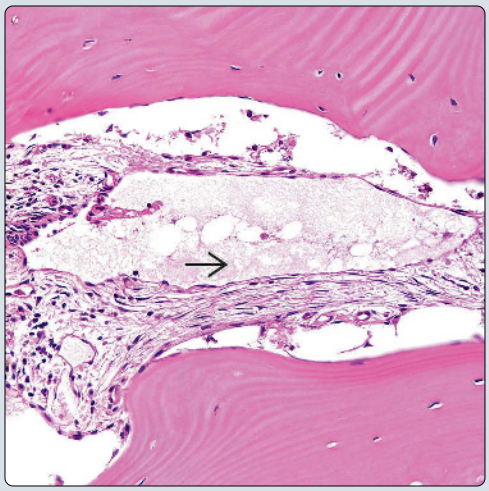


**Well-Circumscribed Lucency**

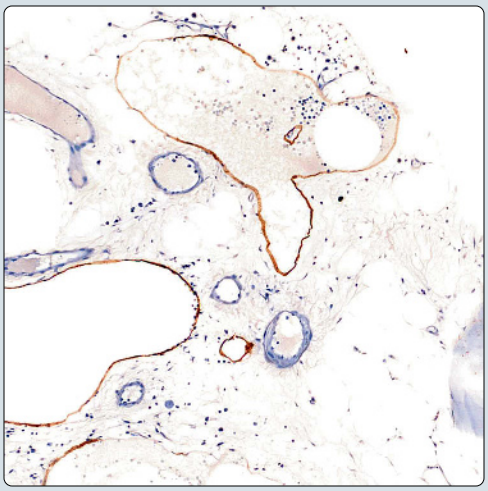


**(Left)** *Lymphangiomatosis of the skeleton in this child presents with multiple lesions in the proximal femora and pelvic bones. The tumors are lytic and tend to have irregular but well-circumscribed margins.* **(Right)** *AP and lateral radiographs of a lymphangioma show a well-circumscribed lucency in the tibia. The tumor involves the medullary cavity and cortex and is surrounded by reactive bone.*

**Thin-Walled Vessel**



**Endothelial Cells Stain With D2-40**



**(Left)** *Lymphangioma vessel is thin walled, lined by flattened endothelium, and filled with proteinaceous fluid ⇨. Note the perivascular lymphocytes.* **(Right)** *The branching lymphatic vessels in this biopsy specimen are lined by endothelial cells that stain strongly with D2-40. The adjacent nonneoplastic vessels have endothelium that are negative.*

## TERMINOLOGY

### Definitions

- Primary benign bone tumor composed of lymphatic vessels

## ETIOLOGY/PATHOGENESIS

### Etiology

- Unknown

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Very rare primary tumor of bone
  - Much less common than hemangioma of bone
- Age
  - Can affect all age groups
  - Most common in young individuals

### Site

- Can involve single bone (lymphangioma) or multiple bones (lymphangiomatosis)
- Unlike hemangioma of bone, lymphangioma rarely involves spine
- Most frequently arise in long bones and craniofacial skeleton

### Presentation

- Patients can present with solitary lymphangioma involving single bone
- Patients may have multiple discrete bone lymphangiomas ± soft tissue involvement (lymphangiomatosis)
- Symptoms depend on extent of disease
- Tumors may arise in bone and soft tissue

### Treatment

- Asymptomatic lesion
  - No treatment needed
- Symptomatic osseous lesion
  - Curettage and packing

### Prognosis

- Very good prognosis when single bone involved
- Prognosis for lymphangiomatosis depends on extent of extraosseous involvement
  - Skeletal lesions can regress with time

## IMAGING

### Radiographic Findings

- Solitary lymphangioma is composed of well-demarcated radiolucent lesion
- Multiple lesions are seen in patients with lymphangiomatosis

### MR Findings

- Nonenhancing lesion(s) containing variably sized cystic spaces
- Low to moderate signal intensity on T1-weighted images
- High signal intensity on T2-weighted images

### CT Findings

- Well-demarcated lesion(s) with low attenuation

## MACROSCOPIC

### General Features

- Sponge-like appearance with cystic spaces filled with clear or straw-colored fluid

## MICROSCOPIC

### Histologic Features

- Vascular spaces may have irregular configuration
- Vessels walls thin and lined by flat endothelial cells
- Vascular lumina filled with proteinaceous fluid
- Red blood cells can be seen in vascular spaces mimicking hemangioma
- Vessels can encase preexisting bone trabeculae

## ANCILLARY TESTS

### Immunohistochemistry

- Endothelial cells may stain with D2-40, CD3, and CD34

## DIFFERENTIAL DIAGNOSIS

### Hemangioma of Bone

- Distinction from hemangioma can be very difficult
- Both are lined by flat endothelial cells
- Vascular spaces are usually filled with blood in hemangioma of bone vs. proteinaceous fluid in lymphangioma
  - Frequently, blood has been washed out in hemangiomas so that they mimic lymphangioma
  - Hemorrhage into lymphangioma can also make distinction difficult
- Both hemangiomas and lymphangiomas stain for endothelial markers
  - Endothelial cells in lymphangioma express D2-40, whereas those in hemangioma are often negative

### Miscellaneous Lesions

- Radiographically, lymphangiomatosis can mimic various multifocal lesions, such as
  - Multifocal eosinophilic granuloma
  - Enchondromatosis
  - Metastatic carcinoma
  - Polyostotic fibrous dysplasia
- All of these tumors are easy to diagnose histologically and differentiate from lymphangiomatosis

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Fragmentation of specimen can make lymphangioma difficult to identify in biopsy specimens
- Possibility of vascular lesion should always be considered when encountering "normal bone" in biopsy specimen

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4. Winterberger AR: Radiographic diagnosis of lymphangiomatosis of bone. Radiology. 102(2):321-4, 1972

# Epithelioid Hemangioma

KEY FACTS

## TERMINOLOGY

- Variant of hemangioma that is composed of plump histiocyte-like or epithelioid endothelial cells

## ETIOLOGY/PATHOGENESIS

- Rearrangement of *FOS* gene common

## CLINICAL ISSUES

- Most commonly arises in long tubular bones (40%)
- Patients usually present with pain localized to involved bone
- Asymptomatic tumors do not need to be treated
- Symptomatic tumors treated with curettage

## IMAGING

- On plain radiograph, lesions are lucent with well-defined margins but can show aggressive features (soft tissue extension)

## MACROSCOPIC

- Grossly, tumors are soft, solid, red, and hemorrhagic

## MICROSCOPIC

- Lobulated growth pattern; can be well demarcated or infiltrative
- Epithelioid endothelial cells are polyhedral in shape and contain abundant densely eosinophilic cytoplasm
- Nuclei are oval or kidney bean-shaped, hyperlobated or cleaved, often bulging into vascular lumina
- Numerous inflammatory cells, including eosinophils and plasma cells, present in stroma
- No hyalinized or myxoid matrix is present

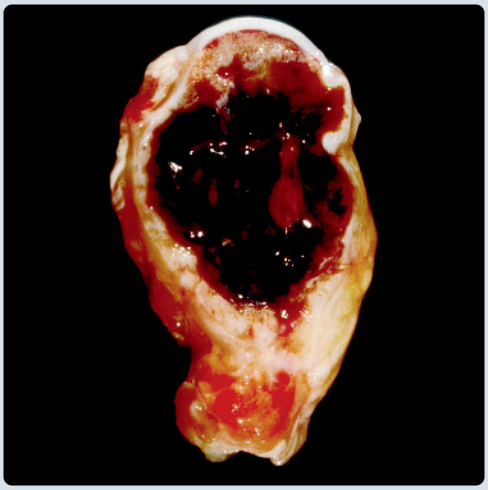
## TOP DIFFERENTIAL DIAGNOSES

- Epithelioid hemangioendothelioma
- Epithelioid angiosarcoma
- Metastatic carcinoma

**Expansile, Lytic Mass**

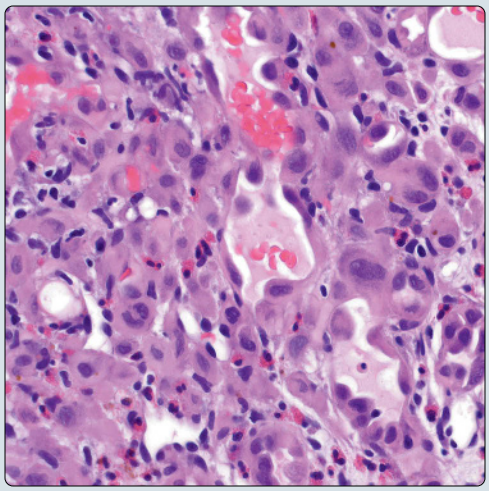


**Hemorrhagic Tumor**

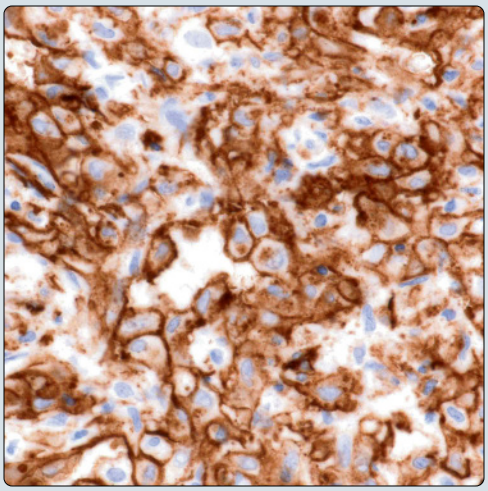


**(Left)** *This epithelioid hemangioma presents as a lytic, expanded, fairly well-defined lesion in the distal 1/3 of the metatarsal extending to the subarticular margin. There is no internal matrix.* **(Right)** *Epithelioid hemangioma involves the distal 1/2 of the metatarsal. The hemorrhagic tumor is solid, well circumscribed, and expands the bone. The tumor extends to the subchondral bone plate.*

**Epithelioid Cells Lining Lumen**



**Strong Staining for CD31**



**(Left)** *Epithelioid cells are growing in solid groups and also line well-formed vascular spaces. The tumor cells have abundant eosinophilic cytoplasm and hyperlobated nuclei. Eosinophils are scattered throughout the tumor.* **(Right)** *The epithelioid cells that line the vascular spaces and grow in solid groups show strong cytoplasmic and membranous staining for CD31.*

## TERMINOLOGY

### Abbreviations

- Epithelioid hemangioma (EH)

### Synonyms

- Histiocytoid hemangioma
- Angiolymphoid hyperplasia with eosinophilia

### Definitions

- Variant of hemangioma composed of plump epithelioid endothelial cells

## ETIOLOGY/PATHOGENESIS

### Genetic Aberration

- Rearrangement of *FOS* gene common
  - Tumors with *ZFP36-FOSB* fusions hypercellular and atypical

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Uncommon variant of hemangioma; incidence is unknown
- Age
  - Occurs in all age groups; most common is 4th decade
- Sex
  - More common in male patients

### Site

- Can involve all bones: Long, flat, and bones of craniofacial skeleton
- Most commonly arises in long tubular bones (40%)
  - Distal lower extremities (18%), flat bones (18%), vertebrae (16%), and small bones of hands (8%)
- ~ 20% have multiple bones involved
- Can arise in skin, soft tissue, and lymph nodes

### Presentation

- Pain localized to involved bone; infrequently incidental finding

### Treatment

- Asymptomatic can be followed; curettage or en bloc excision for symptomatic tumors

### Prognosis

- Recurrences uncommon
- Rare cases of spontaneous resolution reported
- Involvement of regional lymph nodes or other organ systems likely manifestation of multicentric disease

## IMAGING

### Radiographic Findings

- Geographic, lytic with well-defined margins
- May extend into soft tissues
  - Usually occurs in short tubular bones and vertebrae

### MR Findings

- Heterogeneous hypointense signal on T1WI, heterogeneous hyperintense signal on T2WI
- Homogeneous enhancement on gadolinium-enhanced images

### CT Findings

- Lytic with sclerotic margins
- May have honeycomb pattern or appear aggressive with soft tissue extension.

## MACROSCOPIC

### General Features

- Soft, solid, red, and hemorrhagic
  - Relatively well circumscribed, frequently expands bone, can extend into soft tissue

### Size

- 1 to 7 cm in diameter

## MICROSCOPIC

### Histologic Features

- Lobulated growth pattern; well demarcated or infiltrative
- Tumor cells are large, polyhedral, and have abundant densely eosinophilic cytoplasm
  - Frequently contain 1 or more intracytoplasmic vacuoles
    - Vacuoles recapitulate vessel lumen formation, may have intact or fragmented red blood cells
  - Mitoses may be present
- Vacuoles from neighboring cells fuse and create lumina
- Well-formed vessels are numerous, tumor cells bulge into lumen in tombstone or hobnail-like fashion
- Cells can grow in solid cords and sheets
- Nuclei are oval or kidney bean-shaped, hyperlobated or cleaved, and contain fine chromatin
- Stroma may contain eosinophils and plasma cells

## ANCILLARY TESTS

### Immunohistochemistry

- Tumor cells positive for CD31, factor VIII, ERG, and FLI-1; tumor cells can be negative for CD34
- ~ 50% stain for keratin and EMA
  - Staining for these markers can be strong and diffuse

## DIFFERENTIAL DIAGNOSIS

### Epithelioid Hemangioendothelioma

- Tumor cells grow in cords in hyalinized/chondroid stroma
- Exhibit greater degree of cytologic atypia
- Different genetic derangement

### Epithelioid Angiosarcoma

- Severe cytologic atypia and atypical mitoses

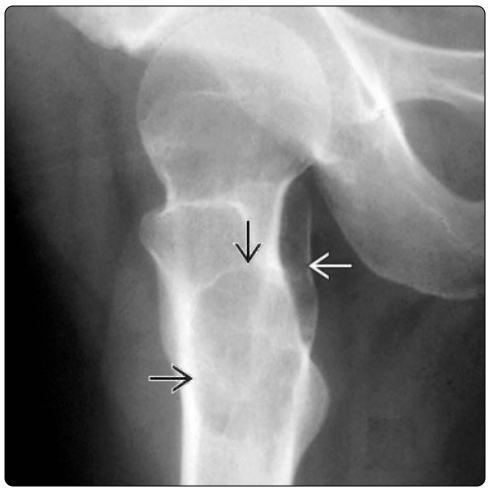
### Metastatic Carcinoma

- Greater cytologic atypia; negative for CD31 and CD34

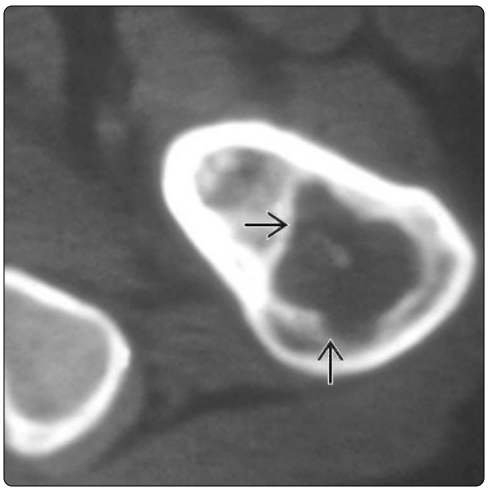
## SELECTED REFERENCES

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2. Nielsen GP et al: Epithelioid hemangioma of bone revisited: a study of 50 cases. Am J Surg Pathol. 33(2):270-7, 2009

**Well-Circumscribed Lytic Tumor**

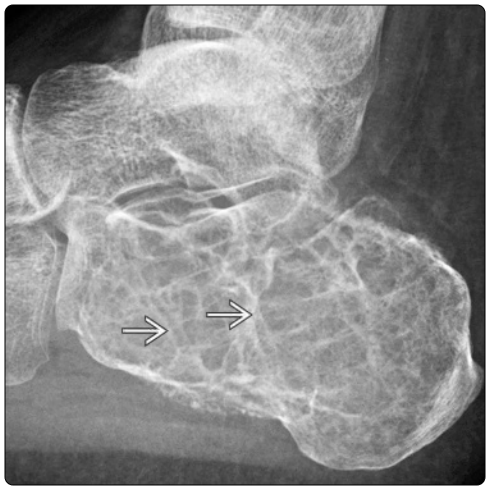


**Lytic Tumor With Sclerotic Margins**



**(Left)** *Epithelioid hemangioma is seen producing a well-defined lytic lesion in the femoral intertrochanteric region. There is minimal cortical expansion present anteriorly and no internal matrix or cortical break.* **(Right)** *Axial CT scan shows an epithelioid hemangioma manifesting as a well-defined lytic lesion in the femoral intertrochanteric region. The margins are sclerotic, and there is no internal matrix. The cortex is intact, and there is not periosteal reaction.*

**Lytic Tumor With Honeycomb Appearance**



**Homogeneous Tumor**

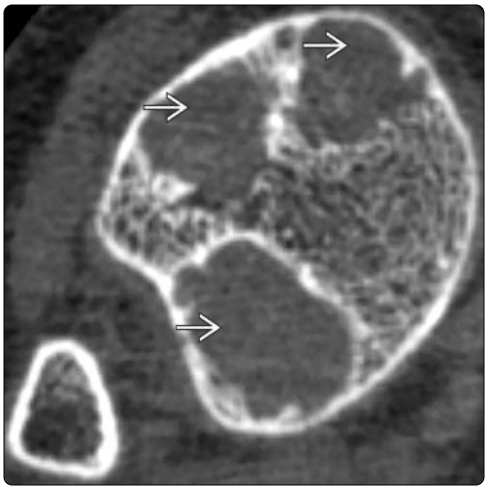


**(Left)** *Lateral view of the ankle shows a large epithelioid hemangioma of the calcaneus that is multiloculated, lytic, and involves the entire bone. The tumor has resulted in expansion of the cortices and is subcompartmentalized by septa of reactive bone.* **(Right)** *Sagittal T1-weighted MR shows an epithelioid hemangioma that replaces the marrow of the entire calcaneus. The tumor has hypointense signal intensity and is confined by the cortex.*

**Numerous Tumors**



**Lytic Tumors With Sclerotic Margins**

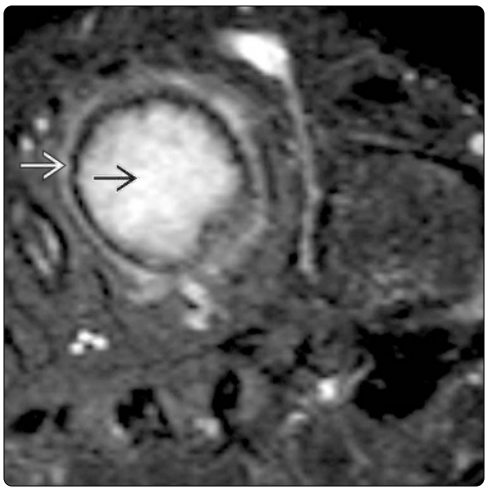


**(Left)** *In this sagittal T1-weighted MR of epithelioid hemangioma, multiple hypointense nodules are present in the distal tibia, talus, other tarsal and metatarsal bones. The lesions are relatively well circumscribed and extend to the subchondral regions of some of the bones.* **(Right)** *Accompanying axial CT with multiple lytic tumors that have sclerotic margins is shown. The cortices are intact, and there is not soft tissue involvement.*

### Expansile, Trabeculated Tumor



### Tumor Filling Medullary Cavity



**(Left)** *An epithelioid hemangioma ⇨ of the 2nd metatarsal expands the distal diaphysis and metaphysis, and it extends to the base of the growth plate ➡. The tumor has a trabeculated lytic appearance with a well-circumscribed and sclerotic margin proximally ⇨.* **(Right)** *Axial T2-weighted MR shows a hyperintense epithelioid hemangioma ⇨ replacing the marrow fat of a metatarsal. A thin rim of hyperintense signal ➡ surrounds the intact cortex.*

### Aggressive Mass



### Intramedullary Nail

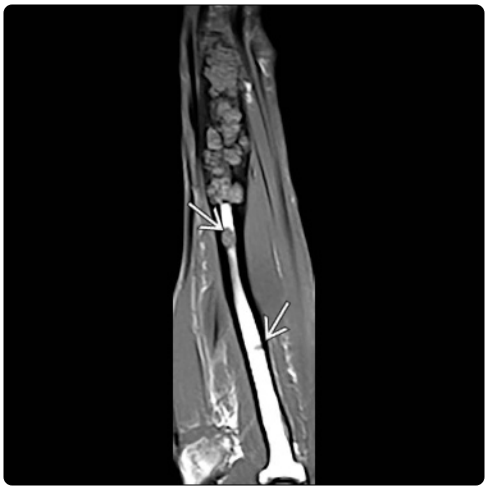


**(Left)** *This epithelioid hemangioma involves the distal femur, proximal tibia, and patella. The tumors are lytic and have margins that range from well circumscribed ➡ to moth-eaten in appearance ➡. The tumors in the femur have resulted in a pathological fracture ⇨.* **(Right)** *Accompanying MR to the previous radiograph is shown. The pathological fracture has been stabilized with an intramedullary nail. There are multiple lytic masses in the femur, tibia, and patella and are centered in the medullary canal and cortex.*

### Multiple Lytic Tumors



### Grape-Like Nodules of Tumor



**(Left)** *There are multiple well-defined lytic tumors that involve the radius and ulna. Most are clustered in the distal radius and expand the bone. Periosteal new bone forms a rim at the periphery of the bulging tumor ➡.* **(Right)** *Accompanying sagittal T1-weighted MR shows the relatively hypointense grape-like aggregates of tumor clustering in the distal radius. Separate lesions are located more proximally in the diaphysis ➡.*

**Lytic Tumor With Sclerotic Margins**

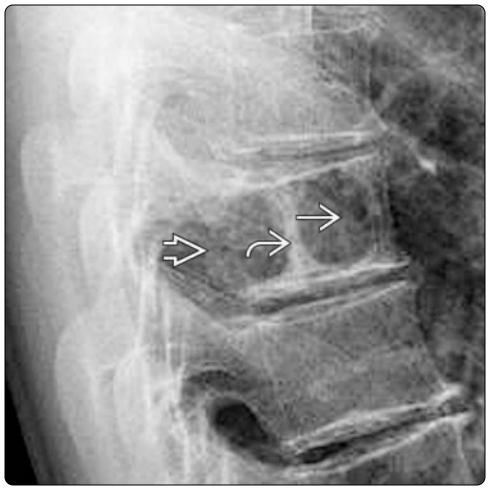


**Cortical Breach**

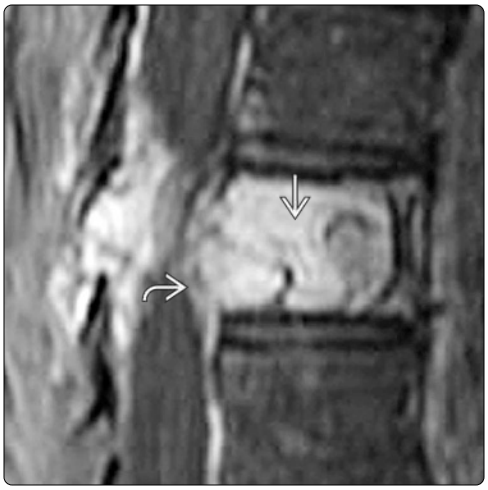


**(Left)** *AP reformatted CT shows an epithelioid hemangioma in the vertebral body with thick sclerotic margins. Within the mass are linear radiodensities, which represent reactive bone. A similar but smaller lesion is noted in the posterior left rib.* **(Right)** *Axial CT scan shows an epithelioid hemangioma involving the left 1/2 of the vertebral body with a separate lesion in the adjacent head of the rib. The lesions are lytic with thick, sclerotic margins.*

**Oval Radiolucencies**

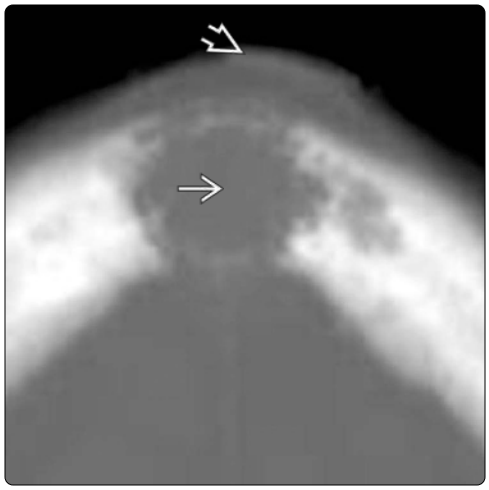


**Destruction of Cortex**



**(Left)** *Lateral view of the thoracic spine shows a lobulated lytic lesion in a vertebral body that is slightly diminished in height. The posterior cortex is expanded and thinned; residual rebuttressed trabeculae are vertical in orientation.* **(Right)** *Sagittal T1-weighted, fat-saturated MR following intravenous gadolinium administration shows an enhancing lesion filling the vertebral body. The posterior cortex is expanded and impinges on the spinal cord.*

**Irregular Margins**

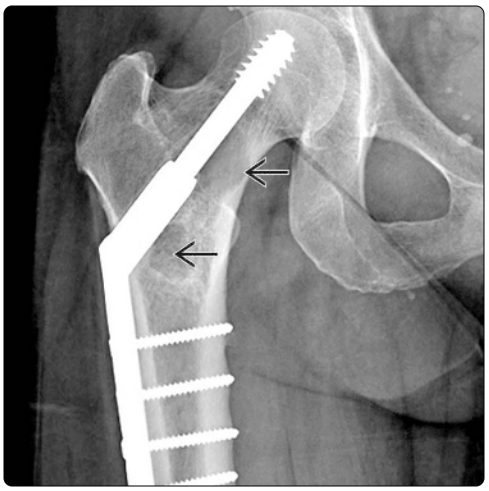


**Oval Mass**

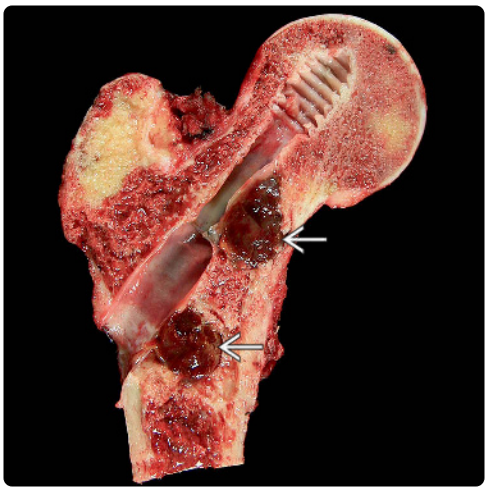


**(Left)** *Epithelioid hemangioma centered in the diploic space of the skull manifests as a destructive lesion with irregular margins. The tumor has eroded the outer and inner tables and produces fullness of the overlying soft tissues.* **(Right)** *Coronal T1-weighted MR following intravenous gadolinium shows an enhancing epithelioid hemangioma in the diploic space. The tumor has transgressed the outer and inner tables but does not involve the brain parenchyma.*

### Painful Hip

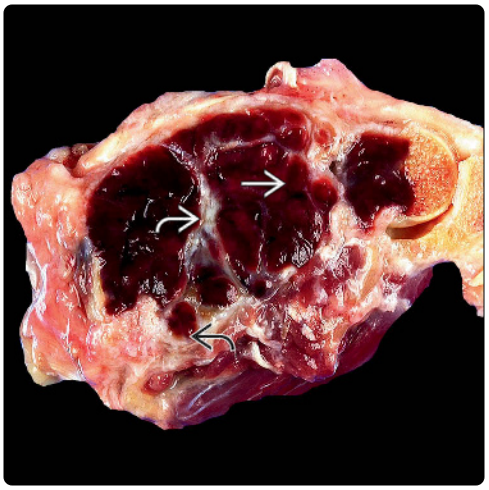


### Well-Defined Hemorrhagic Tumors

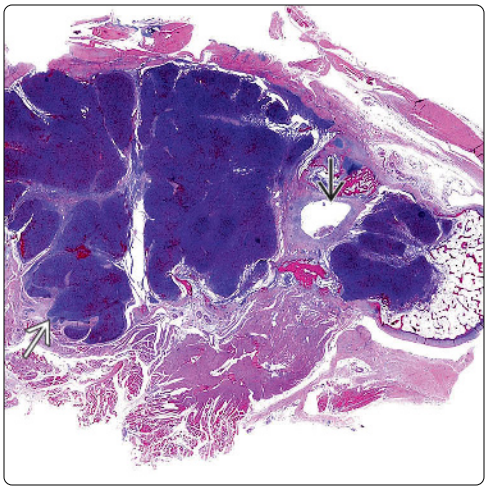


**(Left)** *AP view of the hip shows a dynamic hip screw in place and 2 fairly well-defined lytic nodules of recurrent epithelioid hemangioma in the intertrochanteric femur around the nail, predominantly on the medial side. The tumor was initially treated with a curettage.* **(Right)** *This recurrent epithelioid hemangioma presents as solid, red-tan nodules in the medullary canal adjacent to the tract of a previously placed dynamic screw. The nodules are solid and well circumscribed.*

### Nodular, Red-Brown Tumors

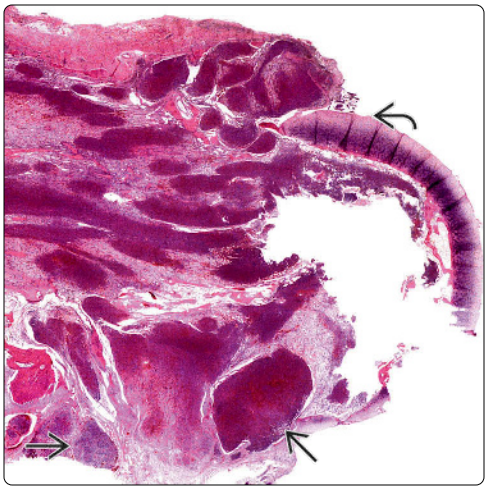


### Lobulated Masses

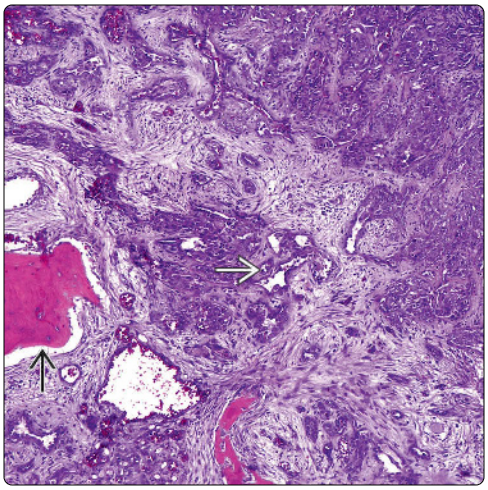


**(Left)** *Epithelioid hemangioma is seen involving most of a proximal phalanx of the foot. The solid red tumor has a nodular architecture formed by white fibrous septa. It is well demarcated, has destroyed the cortex, and bulges into the soft tissues.* **(Right)** *Proximal phalange of the foot is largely destroyed by an epithelioid hemangioma. The tumor has a nodular architecture and extends into the soft tissues. Note the large vessel with which the tumor is associated.*

### Extension Into Soft Tissue

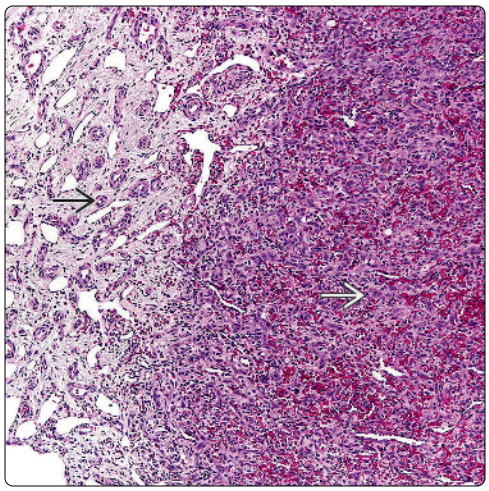


### Organoid Architecture

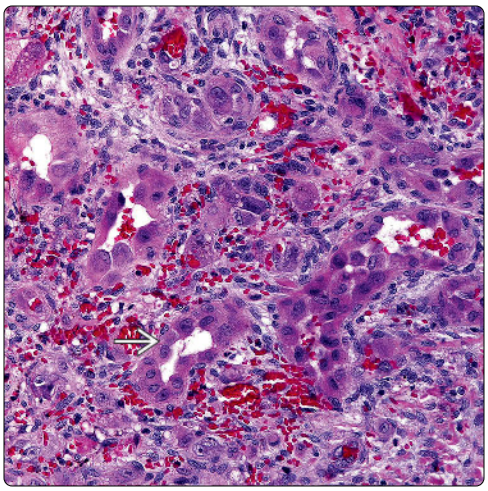


**(Left)** *Epithelioid hemangioma of the 1st metatarsal has a characteristic nodular growth pattern. The tumor has destroyed much of the bone and extends into the soft tissues. The tumor extends up to the subchondral bone plate and the articular cartilage is intact.* **(Right)** *Epithelioid hemangioma involving the medullary cavity replaces the marrow fat and surrounds preexisting bony trabeculae. The tumor is composed of lobules of well-formed branching blood vessels.*

### Small Arterioles

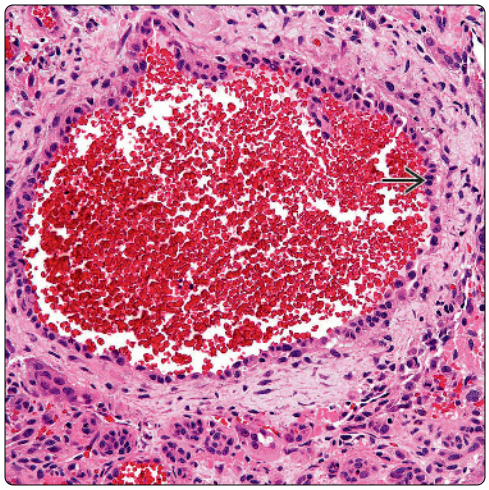


### Well-Formed Vascular Spaces

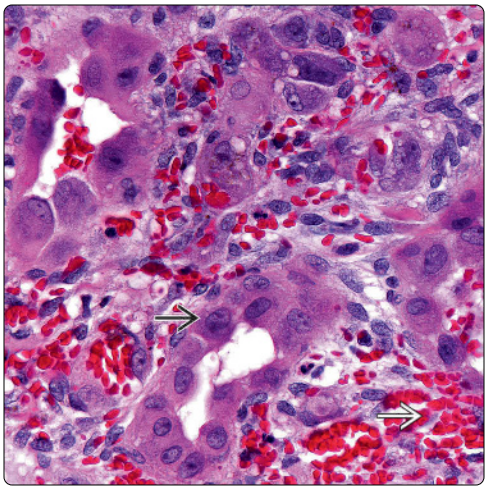


**(Left)** *Lobule of epithelioid hemangioma characteristically composed of a cellular region is surrounded by a collar of loose connective tissue that contains many arteriolar-like structures. The cellular component consists of cords and sheets of proliferating epithelioid endothelial cells.* **(Right)** *Well-formed vessels lined by prominent epithelioid endothelial cells characterize epithelioid hemangioma. The lumina of the vessels are sometimes filled with red blood cells.*

### Dilated Vessel

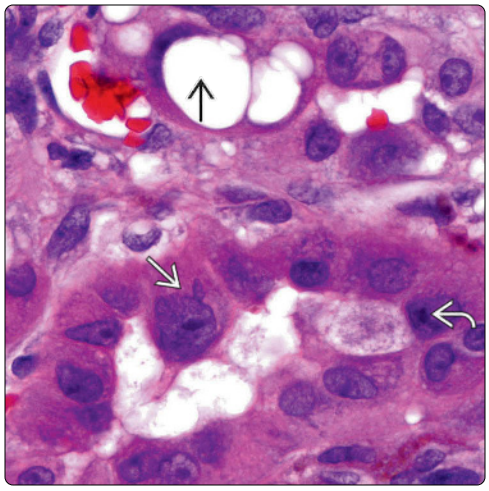


### Densely Eosinophilic Cytoplasm

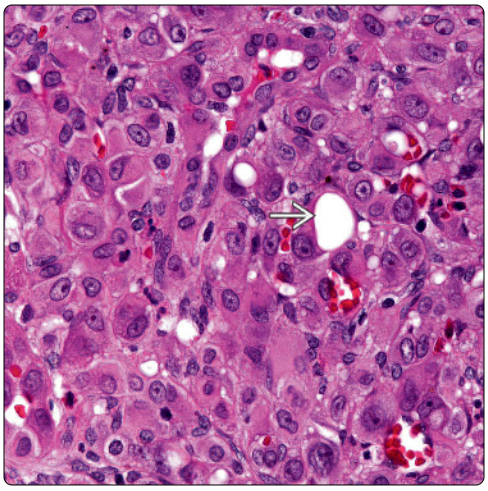


**(Left)** *A minority of epithelioid hemangiomas of bone have a large dilated vessel associated with the mass. When present, the vessel is lined by epithelioid endothelial cells and is surrounded by small caliber neoplastic vessels.* **(Right)** *The neoplastic epithelioid endothelial cells are large and have deeply eosinophilic cytoplasm and round, oval, or kidney bean-shaped nuclei. Notice the extravasated red blood cells in the stroma.*

### Intracytoplasmic Vacuoles

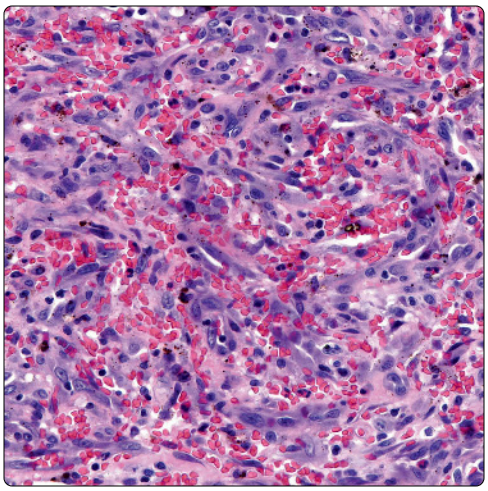


### Sheets of Cells

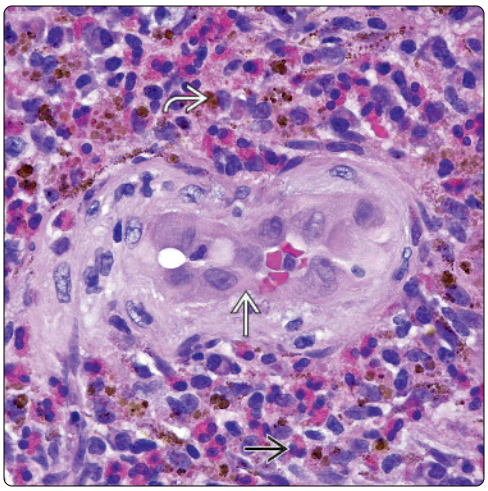


**(Left)** *Epithelioid endothelial cells may contain cytoplasmic vacuoles that fuse with one another and eventually form a luminal space. The tumor cell nuclei may be hyperlobated and contain grooves and prominent nucleoli.* **(Right)** *Epithelioid endothelial cells are seen growing in solid sheets. This degree of hypercellularity is a diagnostic pitfall for more aggressive tumors, such as epithelioid hemangioendothelioma and angiosarcoma. Note the cytoplasmic vacuoles.*

### Spindle Cells

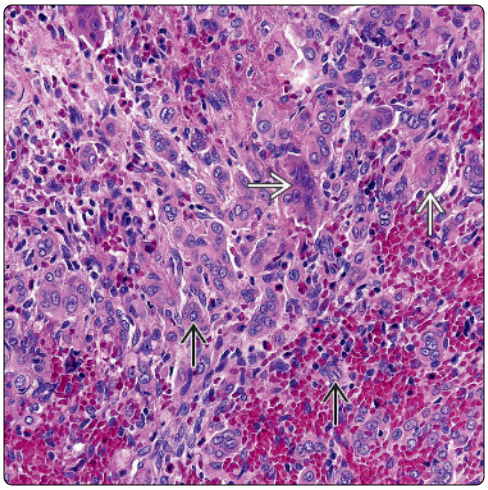


### Numerous Eosinophils

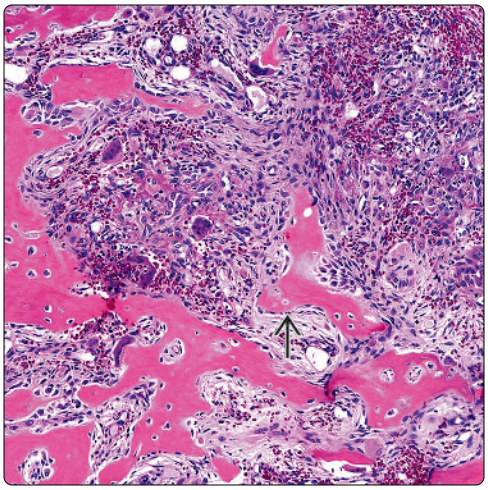


**(Left)** *In some epithelioid hemangiomas, especially those involving the distal lower extremities, the tumor may contain cellular nodules composed of proliferating spindle cells admixed with numerous red blood cells and hemosiderin deposits.* **(Right)** *A dense inflammatory infiltrate rich in eosinophils is another feature of some epithelioid hemangiomas. The proliferating endothelial cells may be obscured by the inflammatory cells. Note the abundant hemosiderin.*

### Many Giant Cells

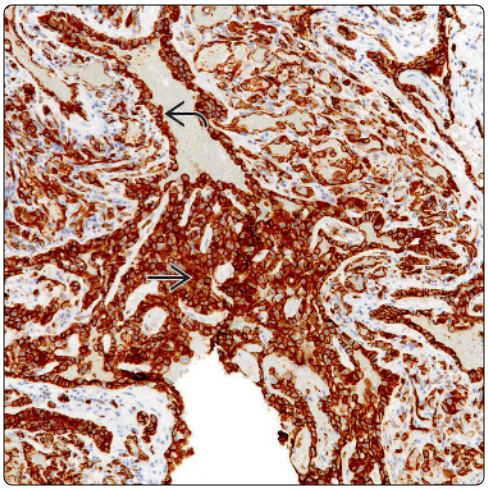


### Reactive Woven Bone

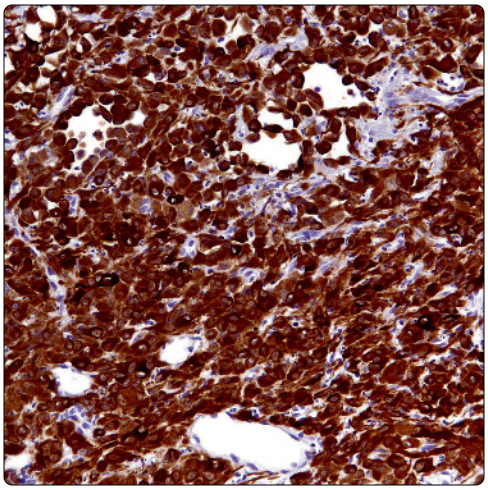


**(Left)** *Epithelioid hemangioma of bone can sometimes have a prominent infiltrate of osteoclast-type giant cells. Their presence can cause confusion with giant cell tumor of bone and aneurysmal bone cyst. The key is the identification of the epithelioid endothelial cells.* **(Right)** *Epithelioid hemangioma may have abundant reactive woven bone that surrounds lobules of tumor. The woven bone may be rimmed with osteoblasts, which can cause confusion with osteoblastoma.*

### Staining for CD31



### Intense Staining for Keratin



**(Left)** *In this case of epithelioid hemangioma that is stained with CD31, the tumor cells are strongly positive and grow in solid clusters and line well-formed blood vessels.* **(Right)** *The epithelioid endothelial cells also may stain intensely with epithelial markers, including keratin (AE1/AE3 in this case) and epithelial membrane antigen, leading to confusion with metastatic carcinoma.*

# Pseudomyogenic Hemangioendothelioma

KEY FACTS

## TERMINOLOGY

- Low-grade malignant endothelial tumor that has specific morphologic features and molecular aberration

## CLINICAL ISSUES

- Progressive localized pain
- Multifocal tumors most commonly affect bones of distal extremity followed by pelvis and spine
- In long bones, tumors are often in diaphysis but may affect metaphysis and epiphysis
- Multifocal tumors may involve 1 or multiple bones

## IMAGING

- Round to oval lytic mass with sharp margins

## MICROSCOPIC

- Well circumscribed; composed of spindle and epithelioid cells
- Most cells are spindled, arranged in loose fascicles
- Spindle cells are plump with densely eosinophilic cytoplasm
- Epithelioid cells have abundant eccentric densely eosinophilic cytoplasm; resemble rhabdomyoblasts
- No lumen formation; cytoplasmic vacuoles uncommon
- Reactive bone; may be abundant and obscure tumor cells
- Osteoclast-like giant cells may be numerous
- Mitotic activity low; small foci of necrosis possible
- Stroma is edematous, thin collagen fibers; rarely chondroid

## ANCILLARY TESTS

- *SERPINE1-FOSB* fusion present in 50%
- Stain intensely for CD31, ERG, FLI-1, keratin AE1/AE3
- Negative for CD34, SMA, desmin; retain INI1

## TOP DIFFERENTIAL DIAGNOSES

- Metastatic carcinoma
- Myogenic tumors
- Giant cell tumor
- Osteoblastoma
- Epithelioid endothelial cell tumors

**Multiple Lytic Lesions**



*In this case of PMH, tumors are present in both the tibia and fibula. The tumors are present in the diaphysis, metaphysis, and epiphysis. They appear as oval and lytic, and some are relatively well circumscribed, and others are moth-eaten in appearance.*

**Multiple Red-Brown Tumors**



*A resected bone contains multiple tumors of PMH, and they appear as red-brown masses. The tumors are located in the medullary cavity and erode the inner aspect of the cortex.*

## TERMINOLOGY

### Abbreviations

- Pseudomyogenic hemangioendothelioma (PMH)

### Synonyms

- Epithelioid sarcoma-like hemangioendothelioma

### Definitions

- Low-grade malignant endothelial tumor that has specific morphologic features and molecular aberration

## CLINICAL ISSUES

### Site

- May be primary in soft tissue (most common), soft tissue and bone, or restricted to bone (least common)
- PMH can arise in any bone
  - Commonly affects long bones, pelvis, and spine
  - Some cases affect short tubular bones, tarsal, and carpal bones
- Tumors can be centered in medullary cavity or cortex
- In long bones, tumors are often in diaphysis but may affect metaphysis and epiphysis
- Multifocal tumors may involve 1 or multiple bones
- Multifocal tumor most often arise in lower extremity (38%) followed by pelvis and spine (28%) and upper extremity (17%)

### Presentation

- Progressive localized pain
- Incidental finding
- Pathologic fracture is uncommon
- Majority of tumors are multifocal at presentation
  - Multifocal tumors are discontinuous and most commonly affect regions of skeleton
  - Tumors may be innumerable in quantity

### Treatment

- Surgical curettage or en bloc resection
- Radioablation performed in select cases
- Observation for asymptomatic tumor or when resection is morbid

### Prognosis

- Very good; tumors may slowly progress or remain stable
  - Visceral metastases are rare

## IMAGING

### Radiographic Findings

- Round to oval, lobulated lytic mass
- Relatively sharp margins
  - Margins may or may not be sclerotic
- Some tumors have moth-eaten appearance

### MR Findings

- Tumors are dark on T1-weighted images and hyperintense on T2-weighted images

### CT Findings

- Well circumscribed and lytic

### PET Scan

- Avid or no uptake; may change over time

## MACROSCOPIC

### General Features

- Pink-tan, dark brown, well circumscribed; 0.1-6.5 cm in size

## MICROSCOPIC

### Histologic Features

- Well circumscribed; spindle and epithelioid cells
  - Most cells are spindled, arranged in loose fascicles
    - Random fascicles or storiform pattern
    - Plump with vesicular nuclei, distinct nucleolus, densely eosinophilic cytoplasm
  - Epithelioid cells have abundant eccentric densely eosinophilic cytoplasm; resemble rhabdomyoblasts
    - Oval vesicular nuclei with nucleoli
    - Isolated or grow in small, solid clusters
  - No lumen formation; cytoplasmic vacuoles uncommon
- Reactive bone; may be abundant, obscure tumor cells
- Osteoclast-like giant cells may be numerous
- Mitotic activity low; small foci of necrosis possible
- Stroma is edematous, thin collagen fibers; rarely chondroid
  - Mixed inflammatory cells and extravasated RBCs

## ANCILLARY TESTS

### Immunohistochemistry

- Stain intensely for CD31, ERG, FLI-1, keratin AE1/AE3, FOSB
- Negative for CD34, SMA, desmin; retain INI1

### In Situ Hybridization

- *SERPINE1-FOSB* fusion present in 50%
  - Reflects balanced t(7;19)(q22;q13)

## DIFFERENTIAL DIAGNOSIS

### Metastatic Carcinoma

- Greater atypia, do not stain for CD31

### Myogenic Tumors

- Stain for muscle markers; negative for CD31

### Giant Cell Tumor

- Lacks cells with densely eosinophilic cytoplasm; different immunoprofile

### Osteoblastoma

- Lacks spindle cell component; different immunoprofile

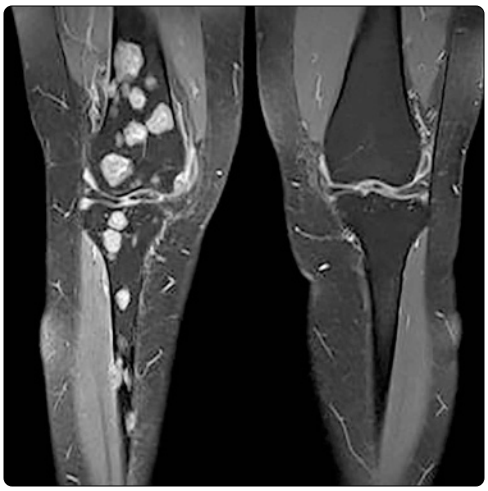
### Epithelioid Endothelial Cell Tumors

- Epithelioid hemangioma is vasoformative; lacks rhabdomyoblast-like cells; different translocation
- Epithelioid hemangioendothelioma: Hyalinized chondroid stroma; different translocation
- Epithelioid angiosarcoma: Greater degree of atypia; different genetic aberrations

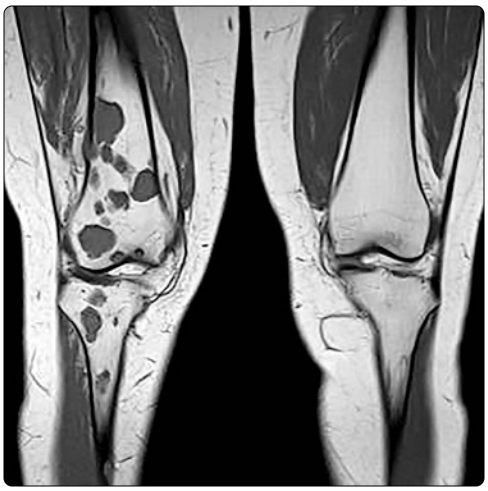
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1. Inyang A et al: Primary Pseudomyogenic hemangioendothelioma of bone. Am J Surg Pathol. 40(5):587-98, 2016

### Many Tumors in Long Bones



### T1-Weighted MR Showing Multiple Tumors



**(Left)** *In this coronal T2-weighted FS MR, multiple bright tumors are present in the medullary cavity of the femur and tibia and erodes the cortex. The other extremity is free of disease.* **(Right)** *Corresponding coronal T1-weighted MR shows the tumors of PMH presenting as round to oval, dark masses present within the medullary cavity.*

### Lytic Lesions



### Numerous Tumors



**(Left)** *This patient with PMH has multiple lytic tumors ➡ involving the distal femoral epiphysis, metaphysis, and diaphysis. The tumor have sharp margins without sclerosis. The proximal femur is not involved.* **(Right)** *This radiograph is from the same patient with the previous radiograph of the tibia. The tumors are innumerable, lytic, well circumscribed, and have sharp margins. The lesions are distributed throughout the bone and involve the medullary cavity and cortex.*

### Lytic Lesions in Spine



### Lytic Tumors of Spine



**(Left)** *Reformatted coronal CT demonstrates multiple round to oval lytic tumors within the medullary cavity of the vertebral bodies ➡. The tumors vary in size and some have focally sclerotic margins.* **(Right)** *PMH presents in this vertebra as lytic lesions in the vertebra and the spinal process. Some of the tumors have a sclerotic margin ➡. One mass erodes the cortex and has eroded the cortex and is confined by reactive bone ➡.*

### Moth-Eaten Bones

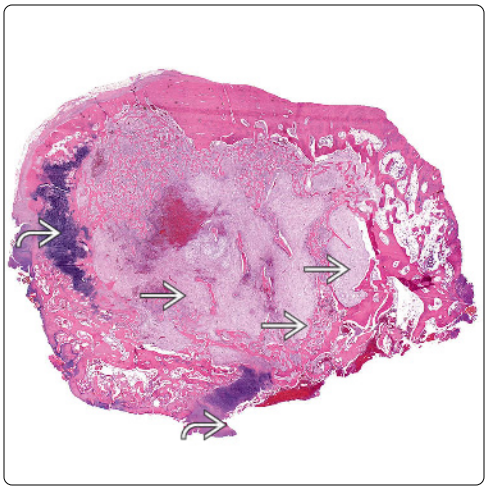


### Intracortical Tumor of Metatarsal

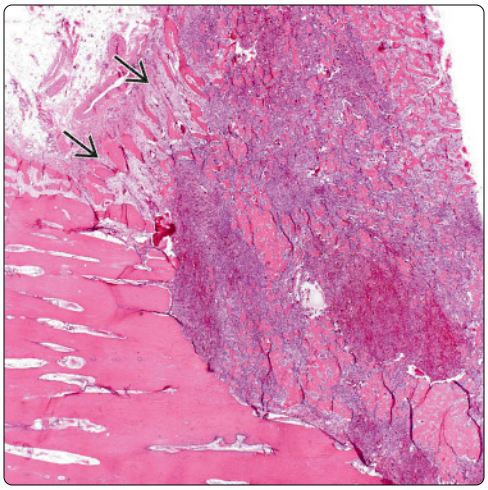


**(Left)** *In this patient with PMH, there are innumerable tumors present in the phalanges, metatarsals, tarsal bones, and distal tibia. The tumors are lytic and moth-eaten in appearance.* **(Right)** *This patient has multiple tumors of the foot, tibia, and femur of the same extremity and underwent an amputation. This mass originates in the cortex of the metatarsal bone and extends into the medullary cavity. The tumor is tan-brown and well circumscribed.*

### Lobulated Mass

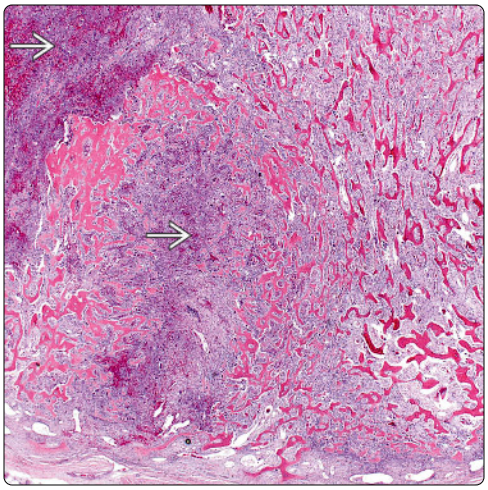


### Well-Circumscribed Mass

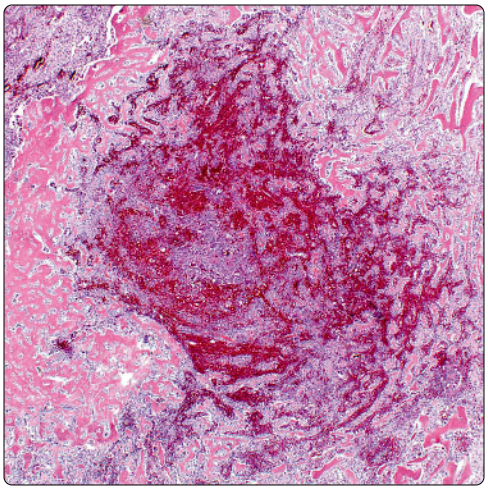


**(Left)** *In this cross section of bone, the PMH has a lobular growth pattern* ➡ *that fills the medullary cavity and is delineated by a rim of reactive bone. The tumor has destroyed the cortex and has caused a pathological fracture with callus composed of cartilage* ➡ *and reactive bone.* **(Right)** *In this example of PMH, the tumor involves the cortex and is well circumscribed. The tumor displaces the cortex, which has deposited reactive woven bone at its periphery* ⇨.

### Lobule of Tumor Surrounded by Bone

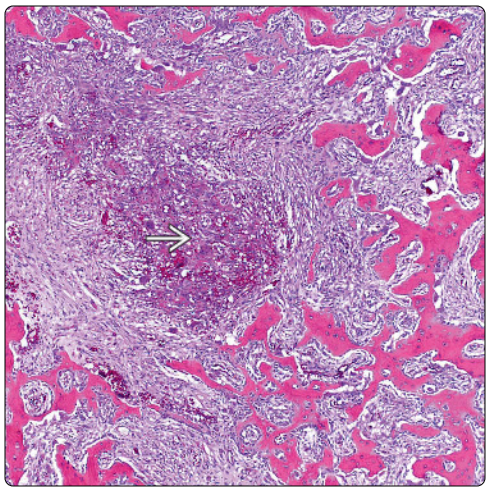


### Hemorrhagic Nodule of Tumor

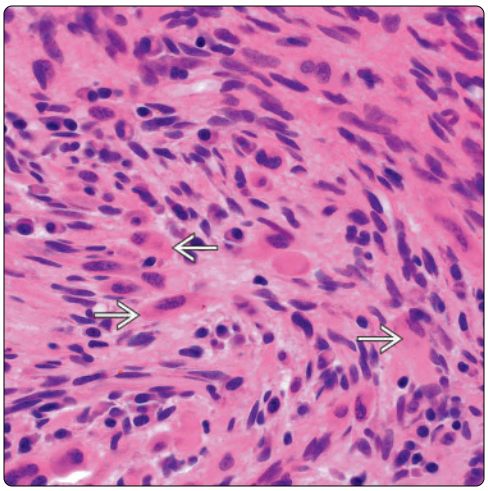


**(Left)** *PMH grows with a lobular architecture. The lobules of tumor* ➡ *are hemorrhagic and are surrounded by septa that contain abundant reactive woven bone.* **(Right)** *The nodules of tumor in PMH often contain abundant extravasated red blood cells. In this example, the nodule of tumor is also surrounded by extensive interconnecting trabeculae of reactive woven bone.*

**Lobule of Tumor**

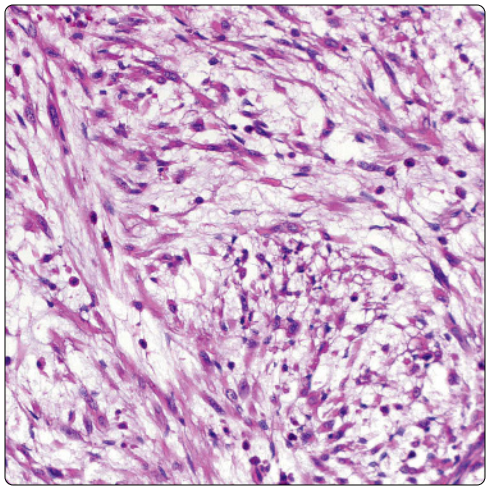


**Spindle and Polyhedral Cells**

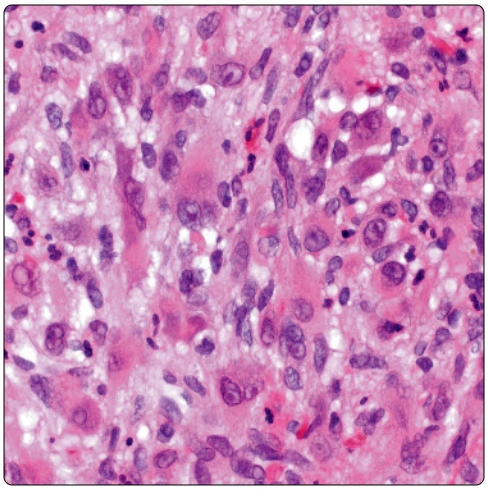


**(Left)** *A lobule of PMH is surrounded by reactive woven bone. In the center of the lobule is a cellular aggregate of neoplastic cells ⇒. The tumor cells and spindled and epithelioid.* **(Right)** *PMH is composed of spindle and polyhedral cells with eosinophilic cytoplasm. The cells with eccentric eosinophilic cytoplasm resemble rhabdomyoblasts ⇒.*

**Fascicles of Spindle Cells**

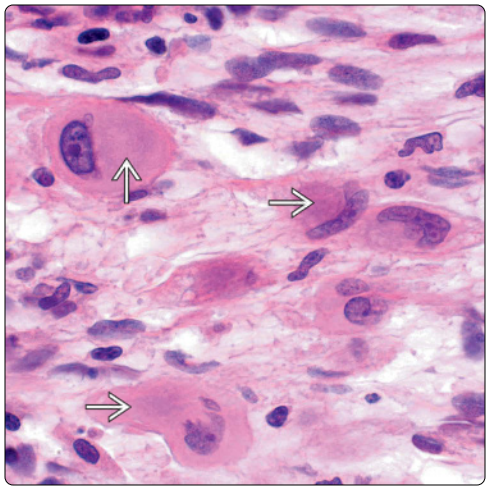


**Spindle and Epithelioid Cells**

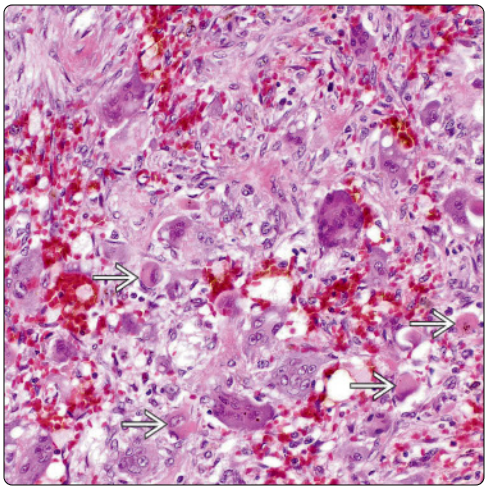


**(Left)** *The tumor cells are plump and spindled and contain densely eosinophilic cytoplasm. The nuclei are elongate and vesicular, and some contain nucleoli. The spindle cells are arranged in intersecting fascicles.* **(Right)** *The tumor cells in PMH are spindled and epithelioid. The cytoplasm of both cell types is densely eosinophilic. The nuclei are vesicular and some have distinct nucleoli.*

**Cells With Abundant Eccentric Cytoplasm**

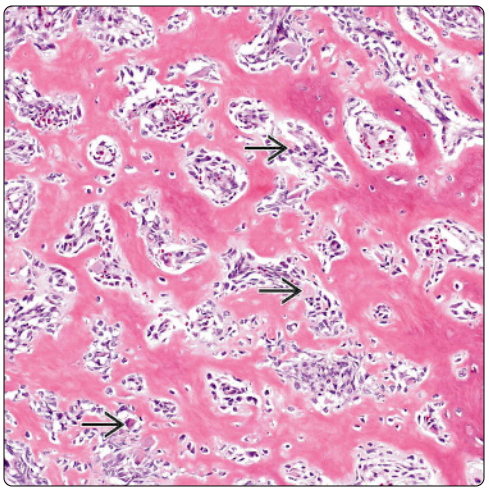


**Many Osteoclasts Obscuring Tumor Cells**

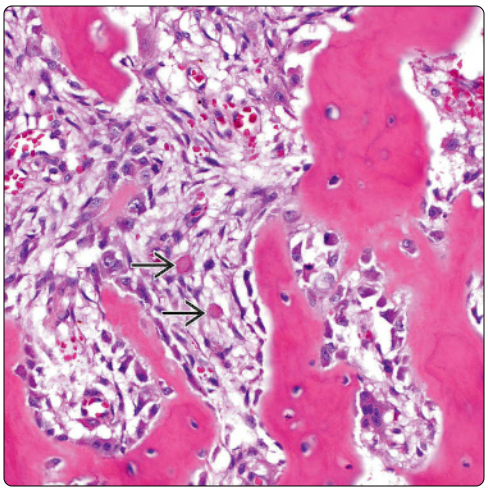


**(Left)** *The cytoplasm of the diagnostic cells is eccentric and and densely eosinophilic ⇒. These cells mimic rhabdomyoblasts and can cause confusion with a variety tumors with myogenic differentiation.* **(Right)** *In some cases of PMH, the tumor contains many osteoclast-like giant cells that obscure the tumor cells that have abundant eccentric eosinophilic cytoplasm ⇒. These foci also contain extravasated red blood cells.*

### Abundant Reactive Woven Bone

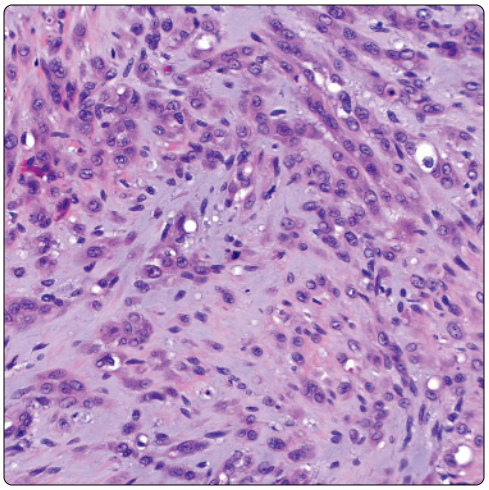


### Tumor Cells Surrounded by Bone

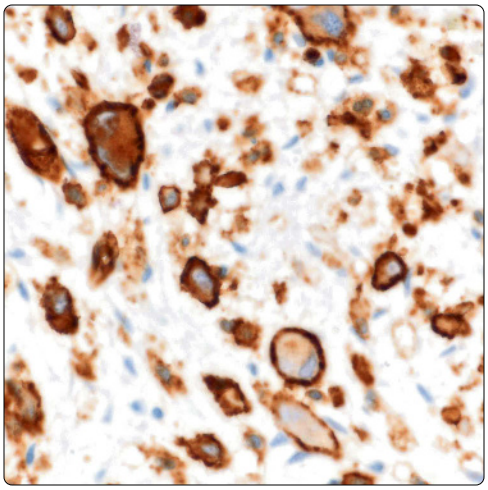


**(Left)** *In some cases of PMH, there is abundant reactive woven bone that obscures the neoplastic cells. In this area, the tumor can be confused with bone-forming tumors.* **(Right)** *Tumor cells with eccentric eosinophilic cytoplasm are surrounded by spindle cells and fill the intertrabecular spaces between the trabeculae of reactive woven bone.*

### Basiphilic Hyalinized Stroma

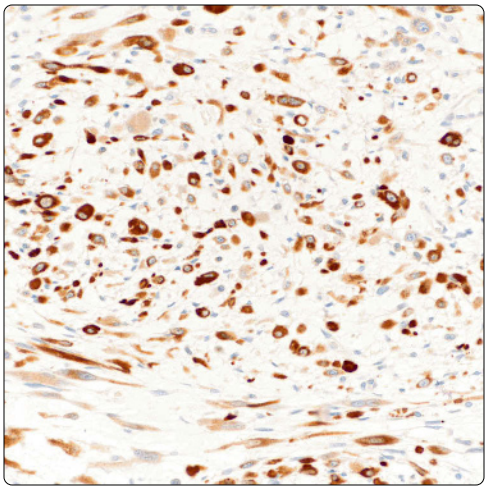


### Tumor Cells are Positive for CD31

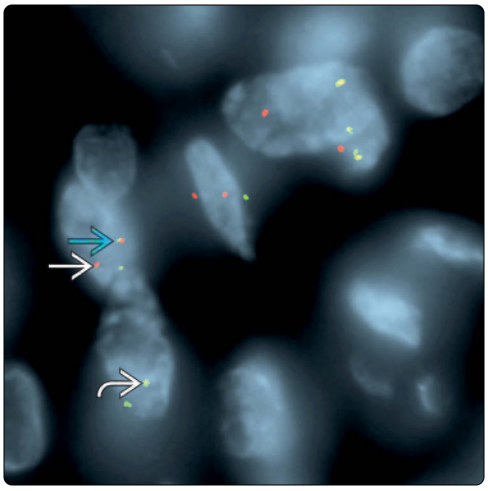


**(Left)** *In a small minority of cases of PMH, the stroma can be basophilic and hyalinized. In these instances the tumor can histologically be identical to EHE. Genetic analysis and immunohistochemistry for CAMTA1 and FOSB can help make the distinction between the 2 types of neoplasms. This tumor had the SERPINE1-FOSB fusion.* **(Right)** *PMH has endothelial differentiation, and the neoplastic cells usually stain strongly for CD31, ERG, and FLI-1. The tumor cells also usually stain for keratin and EMA and do not stain for CD34 or desmin.*

### Strongly Keratin-Positive Tumor Cells



### Joined Signals Indicating Rearrangement



**(Left)** *The tumor cells in PMH are usually strongly positive for keratin, particularly keratin AE1/AE3. The phenomenon can raise the differential diagnosis of metastatic sarcomatoid carcinoma.* **(Right)** *PMH has been shown to have a specific t(7;19) (q22;q13) translocation. This results in fusion of SERPINE1/FOSB genes. In this image, the normal red SERPINE signal is joined to the normal green FOSB gene documenting the fusion.*

# Epithelioid Hemangioendothelioma

KEY FACTS

## TERMINOLOGY

- Uncommon epithelioid endothelial neoplasm with metastatic potential that usually arises in soft tissues, liver, lung, and bones

## ETIOLOGY/PATHOGENESIS

- ~ 90% of epithelioid hemangioendothelioma have *WWTR1-CAMTA1* gene fusion resulting from t(1;3)(p36;q25)

## CLINICAL ISSUES

- Peak frequency: 2nd-3rd decades of life
- Multifocal in 1/3 to 1/2 of patients
- Localized pain and swelling
- Complete surgical excision if feasible

## IMAGING

- Discrete lytic lesions often expansile
- Expansile

## MACROSCOPIC

- Well circumscribed and pale tan color

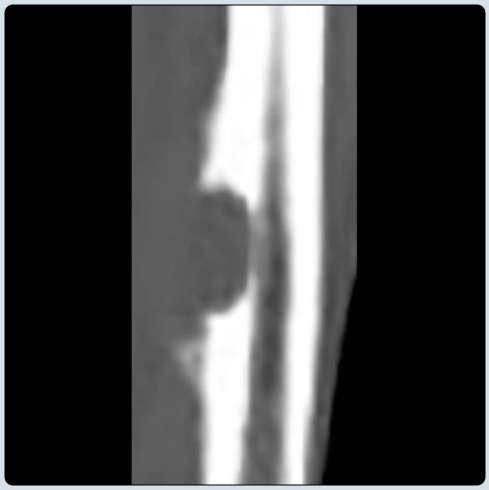
## MICROSCOPIC

- Tumor cells arranged in cords and nests
  - Embedded within myxoid or basophilic to hyalinized ground substance that may resemble cartilaginous matrix
- Large epithelioid and spindle-shaped endothelial cells
- Intracytoplasmic lumina appear as vacuoles
- Shows positivity for CD34, CD31, and FLI-1

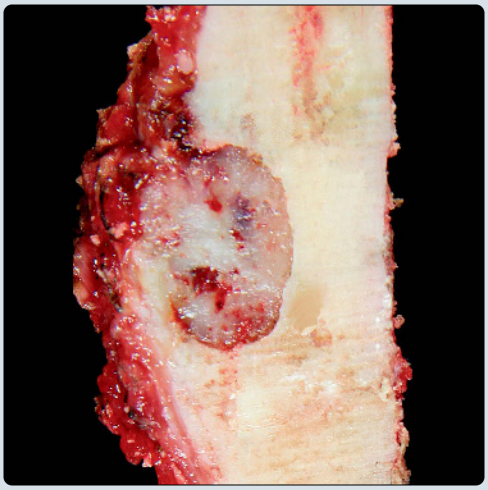
## TOP DIFFERENTIAL DIAGNOSES

- Epithelioid hemangioma
- Epithelioid angiosarcoma
- Metastatic adenocarcinoma
- Chondrosarcoma
- Chordoma
- Bacillary angiomatosis

Intracortical, Lytic Mass

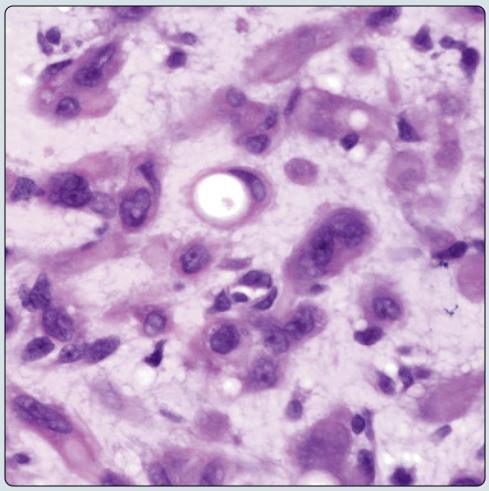


Solid, Tan-White Mass

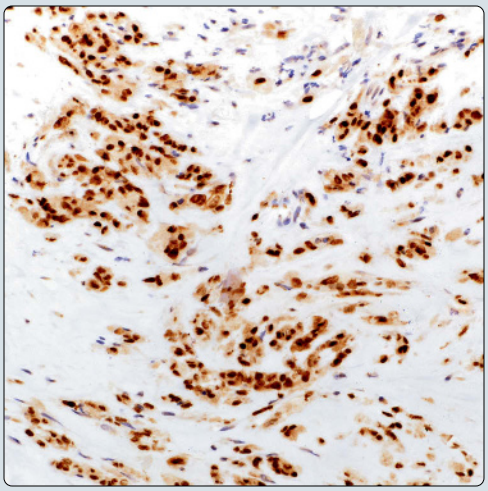


**(Left)** *CT scan shows an epithelioid hemangioendothelioma (EHE) manifesting as a focal, homogeneous, lytic lesion in the cortex. The tumor has well-defined margins, and reactive periosteal new bone is seen proximally and distally.* **(Right)** *EHE of the fibula arises in the cortex and has sharp margins. The tumor is gray-tan-white with small foci of hemorrhage. A rim of subperiosteal reactive bone partially surrounds the mass.*

Cords of Cells With Cytoplasmic Vacuole



Tumor Cells Positive for CAMTA1



**(Left)** *Cords of epithelioid cells are present and have densely eosinophilic cytoplasm. One cell has a prominent intracytoplasmic vacuole that contains a fragment of a red blood cell.* **(Right)** *The tumor cells in this EHE are growing in cords and small solid clusters. They exhibit strong nuclear staining for CAMTA1.*

## TERMINOLOGY

### Abbreviations

- Epithelioid hemangioendothelioma (EHE)

### Synonyms

- Intravascular bronchioloalveolar tumor
- Angioglomoid tumor
- Myxoid angioblastomatosis

### Definitions

- Uncommon epithelioid endothelial neoplasm with metastatic potential that usually arises in soft tissues, liver, lung, and bones

## ETIOLOGY/PATHOGENESIS

### Genetic Aberrations

- ~ 90% have *WWTR1-CAMTA1* gene fusion resulting from t(1;3)(p36;q25)
  - Causes resistance to anoikis and oncogenic transformation of tumor cell+
  - Hippo pathway activated
- ~ 10% have *YAP1-TFE3* fusion gene resulting from t(X;11)(p11;q22)
- Clinicopathological associations with type of translocation
- Controversial whether or not translocations are mutually exclusive

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Rare vascular tumor
    - Exact incidence not known
- Age
  - Can be seen in most age groups
  - Peak frequency: 2nd-3rd decades of life
- Sex
  - No predilection
- Ethnicity
  - Develops in whites disproportionately more often than other races

### Site

- Most frequently arises in soft tissues, liver, lung, and skeleton
- Multifocal in ~ 1/3 to 1/2 of patients
  - Genetic studies that multifocal lesions all share same translocation breakpoint, therefore they are metastases from initial primary tumor
- May involve multiple sites in single bone or multiple bones simultaneously
- Tends to arise in extremities, pelvis, and spine
  - Metaphyseal involvement is typical in long bones
  - Small bones of hands and feet commonly involved
- Patients may also have disease in soft tissues, liver, or lung at time of diagnosis of skeletal disease

### Presentation

- Localized pain
- Swelling
- Pathological fracture

### Treatment

- Complete surgical excision if feasible
- Multifocal lesions may be difficult to excise
  - May be treated with radiation therapy or thermal ablation
- Systemic therapy in select cases

### Prognosis

- Clinical behavior cannot always be predicted by morphologic features of tumor
  - Tumors that demonstrate significant cytologic atypia and increased mitotic activity often behave aggressively
- In one large series, 20% of patients succumbed to disease
  - Of those who died, most had concurrent visceral tumors
- In absence of parenchymal organ involvement, EHE of bone usually behaves in indolent fashion and infrequently metastasizes to other organs
- May locally recur following curettage or slowly enlarge if left untreated

## IMAGING

### Radiographic Findings

- Variable
- Some tumors demonstrate features similar to hemangioma
- Expansile
- Multifocal hemangioendothelioma has appearance of multiple discrete, lytic lesions with intervening bone that appears completely normal
- Round or elongated in shape
- Predominately lytic
  - Rarely can be blastic
- Periosteal reaction is rare
- No mineralized matrix
- Lesions with ill-defined margins and bone destruction are more aggressive

### MR Findings

- May be nonspecific
- Low signal intensity on T1WIs
- High signal intensity on T2WIs
- Adjacent marrow edema may be present
- Homogeneous enhancement with gadolinium

### CT Findings

- Lytic lesion
- Soft tissue density
- Tumor enhances with contrast

## MACROSCOPIC

### General Features

- Pale tan to white in color
- Lacks prominent red, hemorrhagic appearance of conventional hemangiomas
- Well circumscribed; may have scalloped borders
- Nodular architecture
- Solid and infrequently cystic

## MICROSCOPIC

### Histologic Features

- Tumor cells arranged in cords and nests and usually are not vasoformative; often have *WWRT1-CAMTA1* gene fusion
  - Embedded within myxoid or basophilic to hyalinized ground substance that may resemble cartilaginous matrix
- Large epithelioid and spindle-shaped endothelial cells
  - Round or elongated nuclei
  - Prominent nucleoli
  - Abundant eosinophilic cytoplasm
- Intracytoplasmic lumina appear as vacuoles
  - Lumina may contain intact or fragmented red blood cells
- Vacuoles may coalesce to form primitive vascular channels, recapitulating embryonic angiogenesis
  - Well-formed blood vessels not prominent feature in most EHE
- Neoplastic cells generally show limited cytologic atypia
- Mitotic activity is usually low
- In some cases, nuclear hyperchromasia and pleomorphism are significant and mitoses can be numerous
  - These findings make it difficult to distinguish from high-grade angiosarcoma, and distinction may be arbitrary; however, hyalinized/chondroid stroma supports EHE
- Some tumors are vasoformative and composed of large cells with voluminous cytoplasm and mild to moderate cytologic atypia; often have *YAP1-TFE3* gene fusion

### Immunohistochemical Features

- Express full spectrum of immunohistochemical endothelial markers
  - Shows positivity for CD34, CD31, and FLI-1
    - Tumors with *WWRT1-CAMTA1* positive for CAMTA1
    - Tumors with *YAP1-TFE3* positive for TFE3
- Epithelioid endothelial cells may also exhibit intense and extensive positive staining for keratin and epithelial membrane antigen
- Usually do not stain with antibodies to S100 and desmin

### Ultrastructural Features

- Neoplastic cells contain abundant intermediate filaments
- Pinocytotic vesicles
- Intracytoplasmic lumina and pericellular basal lamina material

## DIFFERENTIAL DIAGNOSIS

### Epithelioid Hemangioma

- Lack of hyalinized stroma and paucity of well-formed vessels
  - Both features present in EHE (except for vasoformative variant) but absent in epithelioid hemangioma

### Epithelioid Angiosarcoma

- Lacks hyalinized stroma of EHE
- Shows greater degree of cytologic atypia and mitotic activity

### Bacillary Angiomatosis

- Infectious disease arising in immunocompromised patients
  - Caused by 2 gram-negative bacilli: *Bartonella henselae* and *Bartonella quintana*
- Endothelial cells in bacillary angiomatosis can be epithelioid
  - Do not form cords or nests and are not embedded in chondroid or hyalinized extracellular matrix
    - Stroma contains numerous inflammatory cells
- Organisms can often be seen on Warthin-Starry stain

### Metastatic Adenocarcinoma

- Multifocality of tumor mimics metastatic carcinoma
- Epithelioid features of tumor cells, cohesive nature, and intracytoplasmic vacuoles can also mimic metastatic adenocarcinoma or signet ring carcinoma
  - Staining of tumor cells of EHE for epithelial markers can further complicate this distinction
- Metastatic carcinomas do not stain for endothelial markers, and myxoid or hyalinized stroma is distinct from cellular desmoplastic stroma seen in metastatic carcinoma
- Vacuoles of EHE cells are mucicarmine negative

### Chondrosarcoma

- Extracellular matrix in EHE can mimic chondroid matrix
- Radiographically, chondrosarcoma is not multifocal
- Neoplastic cells in chondrosarcoma do not demonstrate vascular differentiation
- Immunohistochemically, neoplastic cells in chondrosarcoma stain for S100 protein but are negative for endothelial markers

### Chordoma

- Rarely multifocal
- Arise in axial skeleton
- Neoplastic cells in chordoma are cohesive and embedded in extracellular myxoid matrix
- Chordoma cells stain for epithelial markers and brachyury
  - Negative for endothelial markers

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Always consider epithelioid vascular tumor in differential diagnosis of epithelioid tumor in bone
- Epithelioid vascular tumors can be keratin positive but stain for endothelial markers
  - When multifocal, can mimic metastatic carcinoma

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2. Antonescu CR et al: Novel YAP1-TFE3 fusion defines a distinct subset of epithelioid hemangioendothelioma. Genes Chromosomes Cancer. 52(8):775-84, 2013
3. Errani C et al: A novel WWTR1-CAMTA1 gene fusion is a consistent abnormality in epithelioid hemangioendothelioma of different anatomic sites. Genes Chromosomes Cancer. 50(8):644-53, 2011

### Lytic Mass With Periosteal Reaction

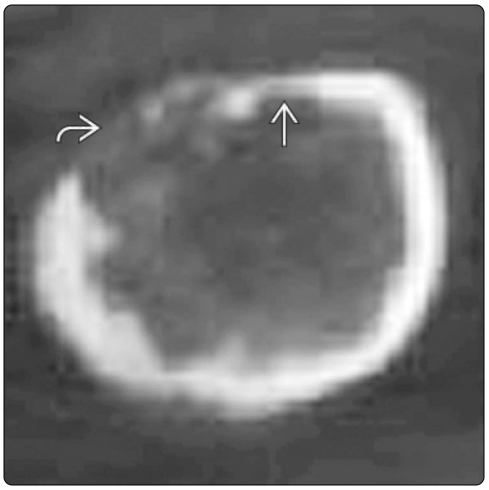


### Lytic Tumor With Irregular Margins

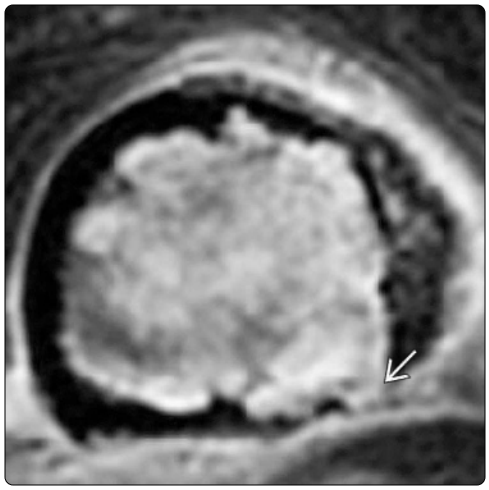


**(Left)** *EHE is shown producing an eccentric, "moth-eaten" lytic lesion in the distal femur. There is thick, periosteal new bone along the medial cortex. The margins are fairly well demarcated.* **(Right)** *Lateral radiograph shows an EHE producing an eccentric, lytic lesion in the distal diaphysis of the femur. The mass erodes the posterior cortex and has induced a thin shell of reactive bone. The tumor is delineated by a subtle rim of sclerosis.*

### Scalloping of Cortex

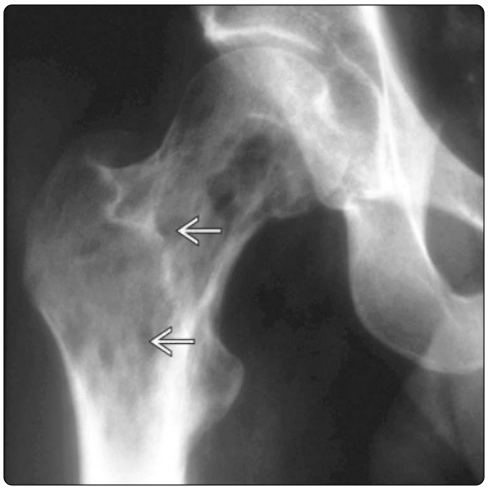


### Erosion of Cortex

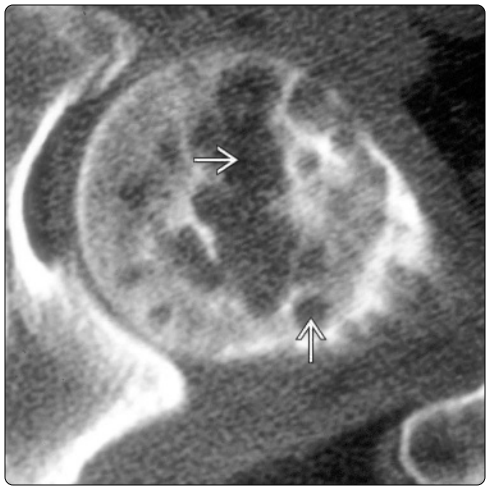


**(Left)** *Axial CT of EHE shows a lytic lesion in the medullary space with nodular scalloping of the inner aspect of the cortex. In some areas, the cortex is severely thinned and focally breached. The soft tissues are unremarkable.* **(Right)** *Axial T2-weighted MR shows hyperintense signal intensity of an EHE that fills the medullary cavity. The tumor has a nodular configuration and erodes the endosteum of the cortex. There is edema in the periosteum and adjacent soft tissues.*

### Multiple Lytic Tumors

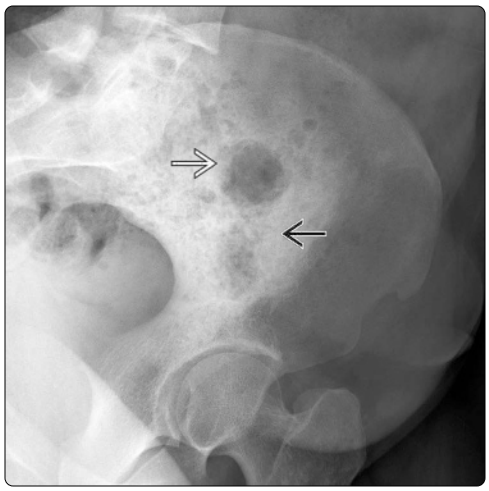


### Numerous Lesions in Femoral Head



**(Left)** *EHE is often multifocal, a phenomenon well illustrated in this radiograph showing multiple well-defined, lytic lesions in the femoral neck and intertrochanteric region. The lesions are relatively small and not associated with a periosteal reaction.* **(Right)** *Axial CT of EHE shows multiple well-defined, lytic lesions in the femoral head with relatively normal-appearing intervening bone. Few lesions are also seen in the acetabulum.*

### Lytic Lesions With Sclerosis



### Marked Bone Sclerosis

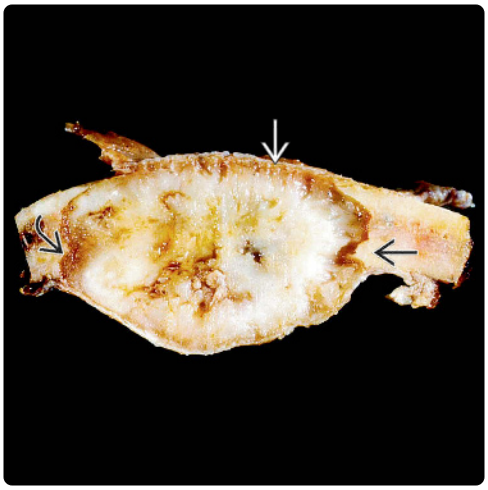


**(Left)** *Oblique radiograph of the left hemipelvis shows an EHE manifesting as a large area distorted by multiple lytic foci of various sizes with reactive bone formation causing surrounding sclerosis. There is no periosteal reaction visible.* **(Right)** *Sagittal reformatted CT of EHE shows a large area affected by multiple lytic lesions of various sizes in the ilium. The tumor expands the bone and is associated with prominent sclerosis.*

### Multifocal Disease

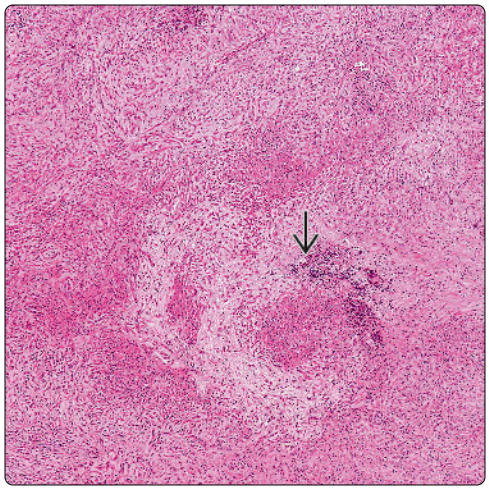


### Solid, Tan-White Mass

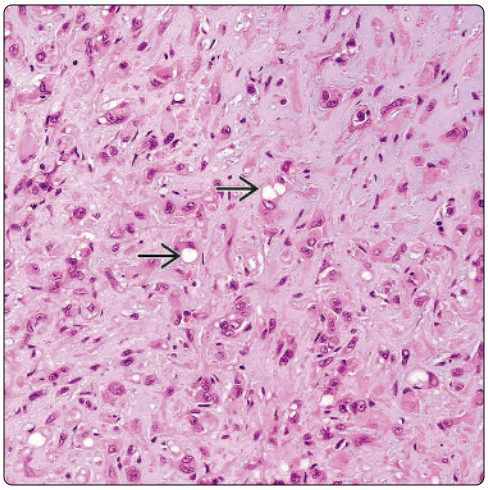


**(Left)** *This EHE was proven to have a YAP1-TFE3 gene fusion and exhibits tumors in the lung and skeleton. The masses in the bone have soft tissue density and are lytic. The tumor in the rib has destroyed much of the surrounding cortex.* **(Right)** *Resected EHE involving the skull shows a solid, tan-white tumor containing small foci of hemorrhage. The tumor has obliterated the diploic space, eroded the outer table, and destroyed the inner table and bulges into the soft tissues. The tumor has sharp margins.*

### Cords of Tumor Cells

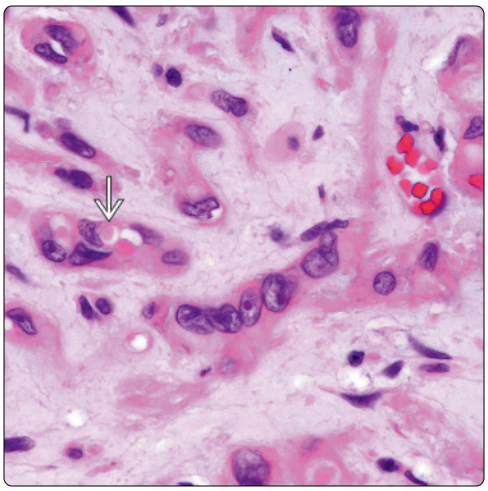


### Hyalinized Basophilic Stroma

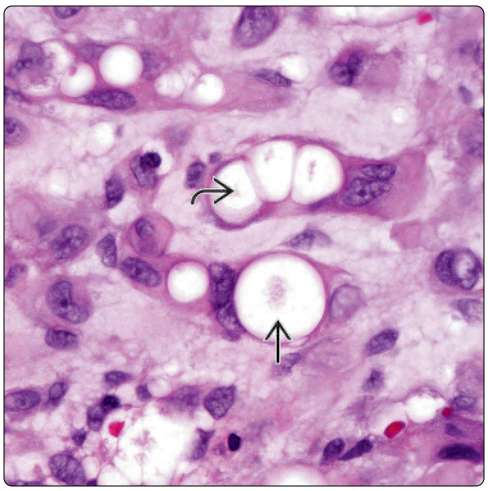


**(Left)** *EHE is solid and composed of cells enmeshed in a variably hyalinized and sclerotic stroma. The tumor cells tend to grow in cords and interconnecting linear arrays. There are small foci of extravasated red blood cells.* **(Right)** *EHE is solid, and the neoplastic cells grow in solid cords. The tumor cells have densely eosinophilic cytoplasm and often contain vacuoles, which represent intracytoplasmic lumina. Note the hyalinized stroma that varies from basophilic to eosinophilic.*

### Vacuolated Tumor Cells

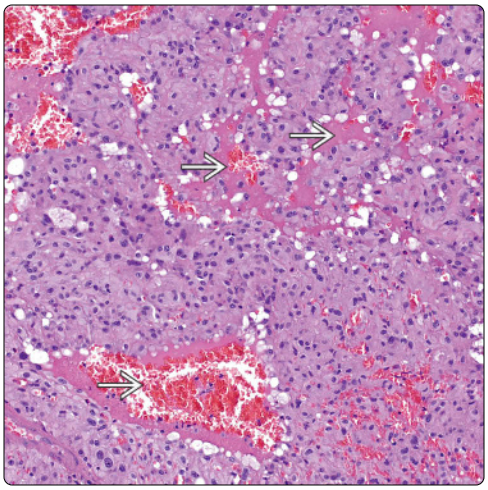


### Fragments of Red Blood Cells

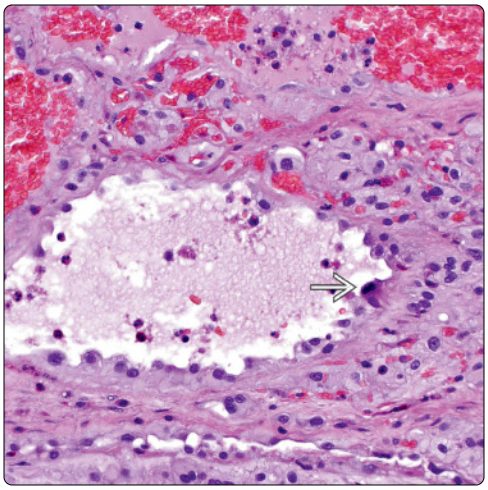


**(Left)** *The tumor cells in an EHE have densely eosinophilic cytoplasm that represents abundant intermediate filaments. Vacuoles containing fragments of red blood cells are present. The stroma is chondroid in appearance.* **(Right)** *Tumor cells in EHE often grow in a linear pattern, and in this case they contain prominent cytoplasmic vacuoles. Within the vacuoles are small portions of red blood cells. Fusion of adjacent vacuoles leads to vessel lumen formation.*

### Vasoformative Tumor

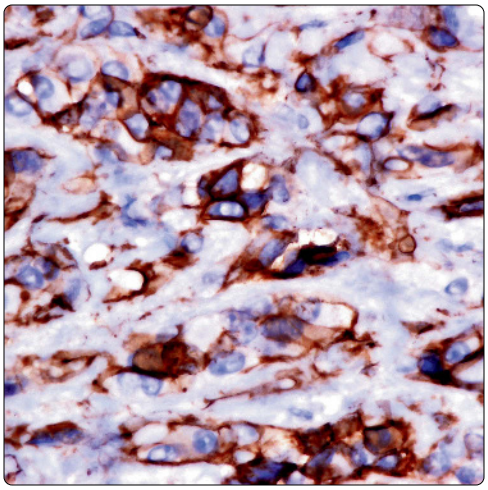


### *YAP1-TFE3* Gene Fusion

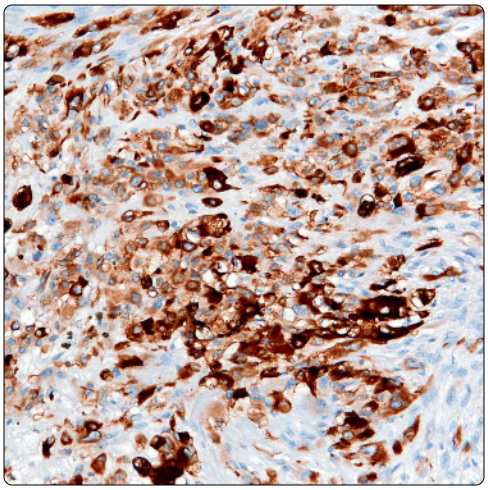


**(Left)** *This EHE has a YAP1-TFE3 fusion and contains many well-formed vascular spaces. The tumor cells are large with abundant densely eosinophilic cytoplasm.* **(Right)** *This EHE has a YAP1-TFE3 fusion and contains well-delineated vascular lumina. Tumor cells protrude into the vascular spaces in a tombstone-like fashion and also grow in small solid clusters.*

### Positive Staining for CD31



### Strong Staining for Keratin



**(Left)** *Tumor cells in EHE express endothelial markers. One of the more sensitive is CD31. Many tumors also stain with antibodies to CD34, ERG, FVIIIRAg, and FLI-1. In this case, the tumor cells show strong cytoplasmic and membrane staining for CD31.* **(Right)** *EHE expresses endothelial markers, including CD31, CD34, and ERG. In ~ 50% of cases, the tumor cells may also stain extensively and intensely with epithelial markers, especially keratin (as in this example) and EMA.*

# Angiosarcoma

KEY FACTS

## TERMINOLOGY

- Uncommon high-grade malignant neoplasm showing endothelial differentiation

## CLINICAL ISSUES

- Accounts for < 1% of primary malignant bone tumors and usually arises in older individuals
- Most angiosarcomas (ASs) are solitary and involve appendicular skeleton
- Up to 1/3 are multifocal and present with involvement of multiple bones
- Usually presents as painful, enlarging mass or pathologic fracture
- Most tumors are high grade and have poor prognosis
- Wide surgical excision
- Adjuvant radiation and chemotherapy

## IMAGING

- Ill-defined, lytic, and destructive mass
- Erodes cortex, periosteal reaction, and invades soft tissues

## MACROSCOPIC

- Dark red and hemorrhagic
- Poorly defined, irregular borders

## MICROSCOPIC

- Cytologically malignant spindle and epithelioid endothelial cells that have capacity to form rudimentary blood vessels
  - Tumor cells can grow in solid sheets or form anastomosing vascular channels
- Epithelioid cells can have intracytoplasmic vacuoles containing red blood cells
- Stain with endothelial markers: CD31, CD34, ERG, and FLI-1
- Epithelioid cells may stain with keratin and EMA

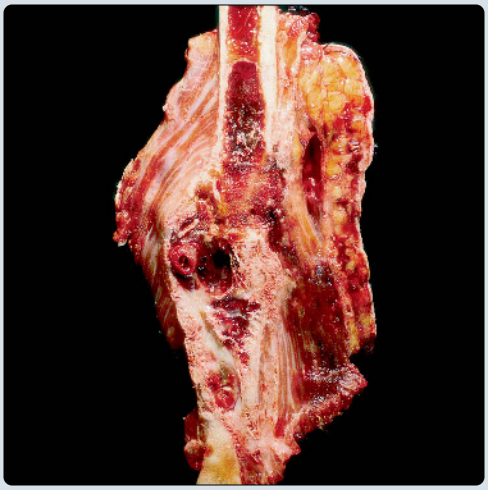
## TOP DIFFERENTIAL DIAGNOSES

- Metastatic carcinoma
- Epithelioid hemangioendothelioma
- Epithelioid hemangioma

**Destructive Mass**



**Hemorrhagic Tumor**

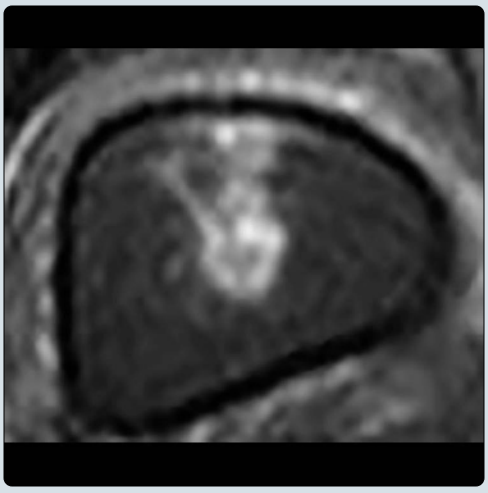


**(Left)** *A pathologic fracture courses through a poorly defined lytic lesion in the distal humeral shaft. The anterolateral cortex is expanded and permeated, and the proximal margin is ill defined.* **(Right)** *Angiosarcoma of the midshaft of the humerus appears as a large, cystic hemorrhagic mass. The tumor has destroyed the bone, causing a pathologic fracture, and extends into the soft tissues.*

**Multiple Tumors**



**Irregular, Bright Tumor in Medullary Cavity**



**(Left)** *In this lateral radiograph of the femur, several oval lytic tumors are present. The multicentric lesions represent angiosarcoma and involve both the medullary cavity and cortex.* **(Right)** *This patient has multiple foci of epithelioid angiosarcoma of the femur. In this axial T2-weighted fat-saturated MR, the tumor appears as an irregular, bright area within the medullary cavity.*

## TERMINOLOGY

### Abbreviations

- Angiosarcoma (AS)

### Synonyms

- Hemangiosarcoma

### Definitions

- Malignant neoplasm showing endothelial differentiation

## ETIOLOGY/PATHOGENESIS

### Neoplastic

- Rarely arises in association with previous radiation, Paget disease, bone infarction, and skeletal hemangiomatosis

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Accounts for < 1% of primary malignant bone tumors
- Age
  - Usually older individuals; 2nd-8th decades of life
- Sex
  - Slightly more common in males

### Site

- Usually solitary and involve appendicular skeleton
  - 1/3 are multifocal and involve multiple bones

### Presentation

- Painful, enlarging mass
- May cause pathologic fracture

### Treatment

- Wide surgical excision
- Adjuvant radiation and chemotherapy

### Prognosis

- Prognosis is related to degree of differentiation
- Most tumors are high grade and have poor prognosis

## IMAGING

### Radiographic Findings

- Ill-defined, lytic, destructive mass similar to nonmatrix-forming sarcomas
- Erodes cortex, periosteal reaction, and invades soft tissues

### MR Findings

- Delineates extent and relationship to adjacent neurovascular bundle
- Lesions enhance with gadolinium
- Soft tissue extent well visualized

### CT Findings

- Confirms invasive and permeative features

### Bone Scan

- May not show uptake except along margins

## MACROSCOPIC

### General Features

- Dark red and hemorrhagic
- Poorly defined and infiltrates soft tissues
- Tumor necrosis may be prominent

### Size

- From 2 cm to > 10 cm

## MICROSCOPIC

### Histologic Features

- Malignant spindle or epithelioid cells that form blood vessels
  - Can grow in solid sheets or form vascular spaces
- Epithelioid variant is composed of malignant epithelioid cells
  - Some cells have cytoplasmic vacuoles that may contain red blood cells
- Numerous mitoses with atypical forms
- Stroma is inconspicuous
- Neutrophilic infiltrate may be prominent
- Cystically dilated, blood-filled spaces with areas resembling papillary endothelial hyperplasia

### Immunohistochemical Features

- Stain with endothelial markers: CD31, CD34, ERG, and FLI-1
- Epithelioid cells may stain with keratin and EMA

## ANCILLARY TESTS

### Genetic Testing

- May have mutations in *PLCG1* and *KDR* genes and amplification of *MYC*

## DIFFERENTIAL DIAGNOSIS

### Metastatic Carcinoma

- Carcinoma can mimic epithelioid AS clinically and pathologically
  - Carcinoma does not stain for CD34 and CD31

### Epithelioid Hemangioendothelioma

- Epithelioid hemangioendothelioma contains hyalinized or chondroid stroma absent in AS; there may be overlap in cytologic features

### Epithelioid Hemangioma

- Does not demonstrate significant cytologic atypia and has limited mitotic activity

## DIAGNOSTIC CHECKLIST

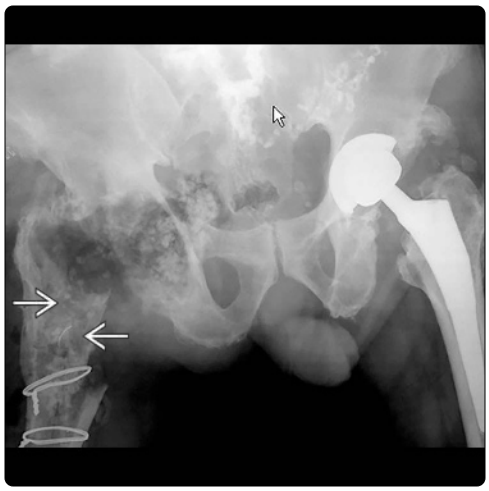
### Pathologic Interpretation Pearls

- Consider AS for keratin (+) malignant epithelioid neoplasm

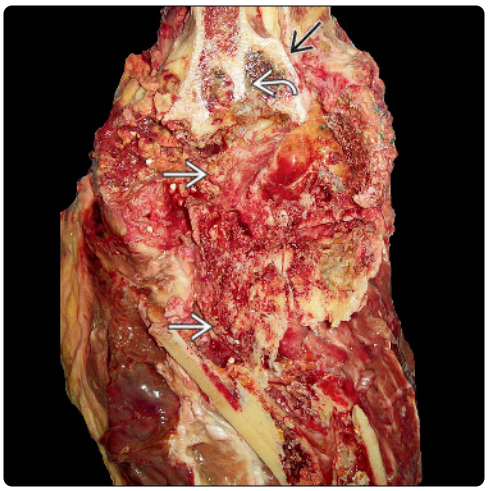
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2. Palmerini E et al: Primary angiosarcoma of bone: a retrospective analysis of 60 patients from 2 institutions. Am J Clin Oncol. 37(6):528-34, 2014
3. Deshpande V et al: Epithelioid angiosarcoma of the bone: a series of 10 cases. Am J Surg Pathol. 27(6):709-16, 2003

### Angiosarcoma Associated With Prosthesis



### Hemorrhagic Tumor

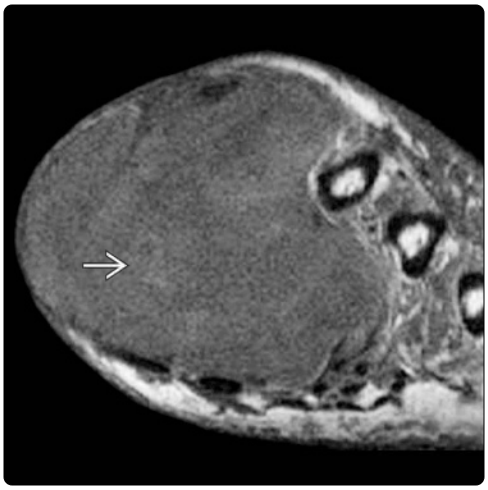


**(Left)** *Patient had bilateral total hip prostheses. Right prosthesis loosened & was associated with surrounding bone lysis. Pathological fracture occurred & prosthesis was removed. Tumor manifests as a lytic destructive mass ➡. (Right) Hind-quarter amputation for an angiosarcoma arose adjacent to a hip joint prosthesis. Hemorrhagic & cystic tumor ➡ has destroyed the ilium & femur adjacent to the prosthetic components. Solid areas of neoplasm ➡ expand the ilium & are surrounded by subperiosteal bone ⇨.*

### Large Destructive Mass

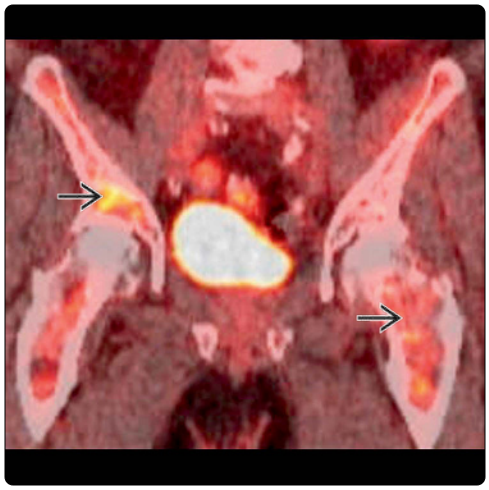


### Large Mass



**(Left)** *An expansile, lytic tumor destroys much of the 1st metatarsal, leaving behind small fragments of preexisting bone ➡. The proximal margin shows thin, periosteal reactive bone. There is swelling of the adjacent soft tissues.* **(Right)** *Axial T1-weighted MR shows a large heterogeneous soft tissue mass replacing the medial metatarsal and extending into the adjacent tissues, obliterating the medial subcutaneous tissue. The hyperintense areas ➡ may represent blood products.*

### Multiple Areas of Uptake

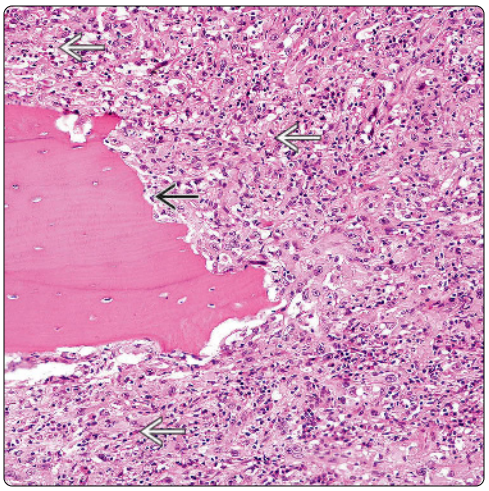


### Numerous Lytic Masses

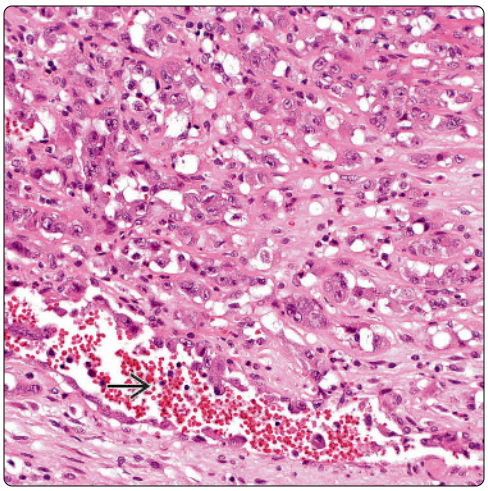


**(Left)** *Coronal PET/CT fused image shows FDG uptake ⇨ of several deposits of angiosarcoma within the iliac bones and proximal femora. This type of distribution raises the possibilities of other tumors, including metastatic carcinoma.* **(Right)** *Axial CT of the pelvis in a patient who has widely disseminated angiosarcoma is shown. Nodules of lytic tumor are present throughout the left and right ilia ➡.*

### Infiltrative Tumor Eroding Bone

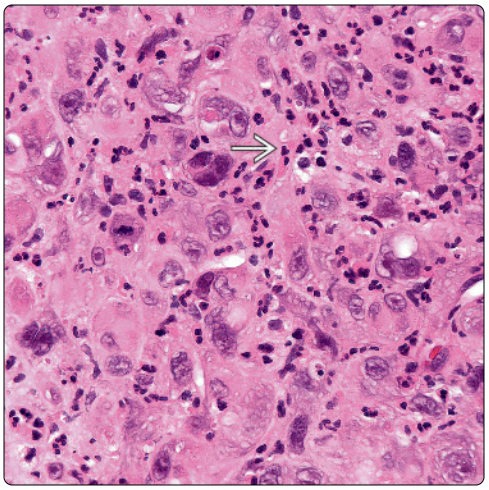


### Sheets of Epithelioid Cells

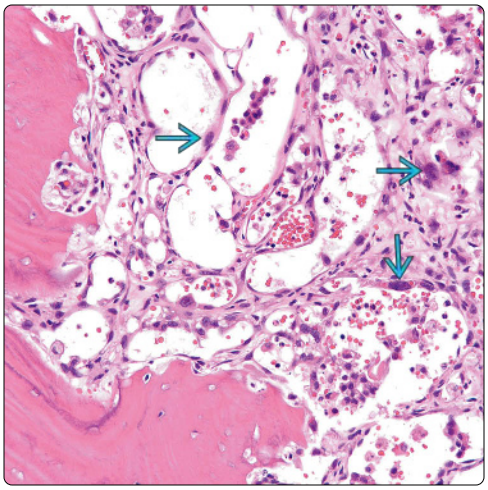


**(Left)** *Epithelioid angiosarcoma replacing the marrow and encasing a bony trabeculum is shown. Osteoclasts are resorbing the bone along the advancing edge of the tumor.* **(Right)** *The tumor cells in epithelioid angiosarcoma grow in solid clusters and cords and focally form well-defined vascular lumina that contain red blood cells. The tumor cells grow in a collagenous stroma.*

### Epithelioid Cells

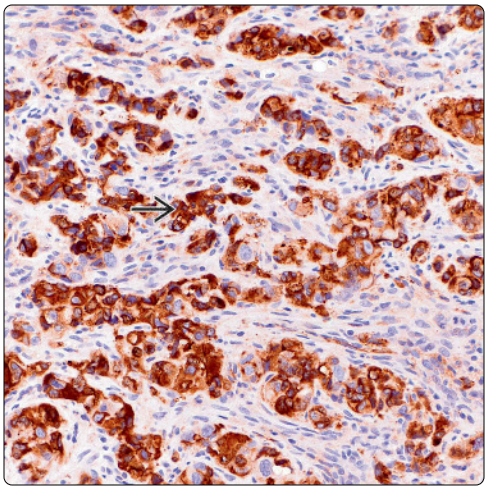


### Multiple Vascular Spaces

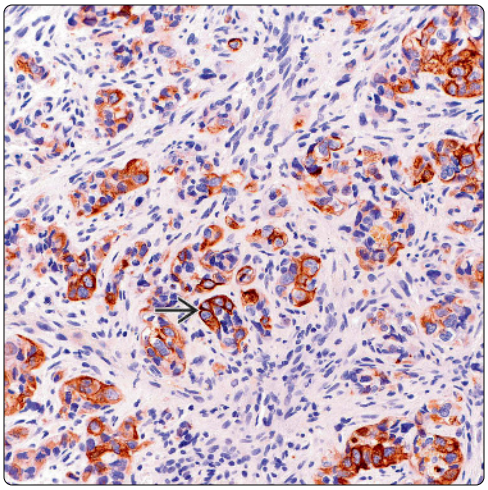


**(Left)** *Epithelioid angiosarcomas are composed of very large round and oblong cells with abundant densely eosinophilic cytoplasm. The nuclei are irregularly lobated, range from vesicular to hyperchromatic, and have prominent nucleoli. Note the presence of neutrophils.* **(Right)** *Angiosarcoma replaces the marrow cavity and grows with an infiltrative pattern resulting in resorption of the bone. The vascular spaces are lined by cytologically malignant cells.*

### Groups of Cells Stained With CD31



### Strong Staining for Keratin

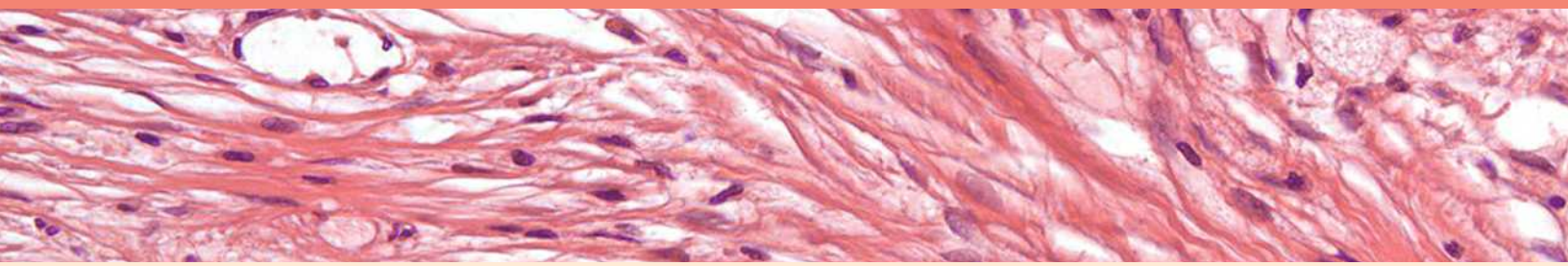


**(Left)** *CD31 is strongly expressed in the cytoplasm of the epithelioid angiosarcoma cells. The staining highlights the arrangement of the tumor cells in solid aggregates and cords.* **(Right)** *Epithelioid angiosarcoma expresses epithelial markers in ~ 50% of cases. In this example, the tumor cells exhibit strong staining for keratin. As angiosarcoma frequently develops in older individuals, this staining pattern can cause confusion with metastatic carcinoma.*

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SECTION 12

# Hematopoietic Tumors




| | |
|---|---|
| Langerhans Cell Histiocytosis (Eosinophilic Granuloma) | **346** |
| Primary Lymphoma | **352** |
| Plasma Cell Myeloma | **360** |
| Mast Cell Disease | **368** |
| Erdheim-Chester Disease | **370** |
| Rosai-Dorfman Disease | **376** |

# Langerhans Cell Histiocytosis (Eosinophilic Granuloma)

KEY FACTS

## TERMINOLOGY

- Eosinophilic granuloma
- Histiocytosis X
- Intraosseous neoplastic proliferation of Langerhans cells

## CLINICAL ISSUES

- Usually diagnosed during first 3 decades of life
- Can develop in any bone but most common in skull and jaw
- Monostotic disease usually managed by curettage or by direct intralesional injection of corticosteroids
- Patients with monostotic skeletal involvement have excellent prognosis
- Multifocal systemic disease has guarded prognosis

## IMAGING

- Well-defined lytic lesion
- Cortical involvement may elicit periosteal reaction

## MICROSCOPIC

- Cells have eosinophilic cytoplasm and contain central ovoid, coffee bean-shaped, indented nuclei that have pale chromatin and inconspicuous nucleoli
- Eosinophils are distributed evenly or arranged in clusters, producing eosinophilic abscesses
- Langerhans cells strongly express CD1a, S100 protein, and langerin

## ANCILLARY TESTS

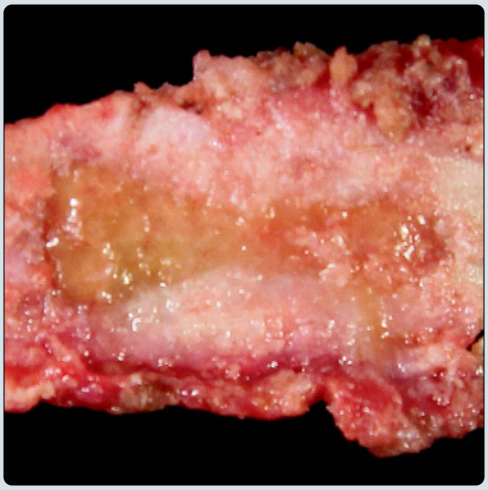
- Birbeck granules are tubular pentalaminar membrane-bound cytoplasmic organelles; frequently have terminal oval protrusions resembling tennis racket or lollipop

## TOP DIFFERENTIAL DIAGNOSES

- Acute and chronic osteomyelitis
- Skeletal diseases with increased eosinophils

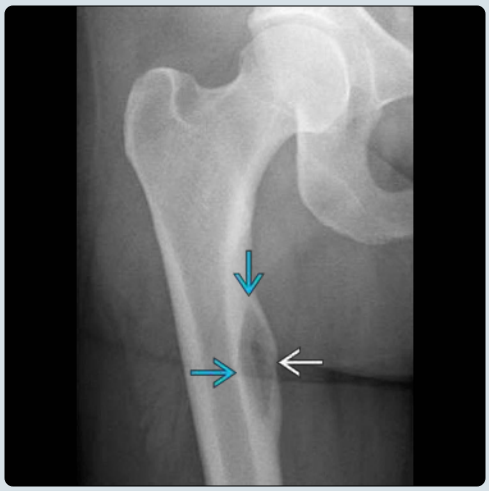
**Lytic Lesion Involving Radius** | **Solid Tumor Involving Rib**

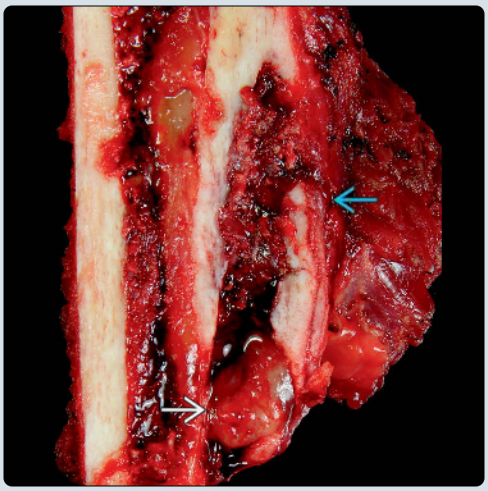




**(Left)** *Radiograph of Langerhans cell histiocytosis shows a lytic, expanded lesion in the proximal radius with endosteal resorption and expansion of the anterior and posterior cortices.* **(Right)** *In this eosinophilic granuloma arising in the rib, the tumor is centered in the medullary cavity. It is lobulated and tan-yellow. The surrounding bone is thickened.*

**Intracortical Lesion** | **Hemorrhagic Intracortical Lesion**





**(Left)** *Intracortical Langerhans cell histiocytosis is shown. The tumor involves the diaphyseal cortex of the femur. It is oval, and well demarcated with what appears to be a small fracture.* **(Right)** *Corresponding gross image of the resected intracortical Langerhans cell histiocytosis is shown. The tumor is hemorrhagic with a more solid tan area inferiorly. There is a focal break in the cortex.*

## TERMINOLOGY

### Abbreviations

- Langerhans cell histiocytosis (LCH), eosinophilic granuloma (EG)

### Synonyms

- Histiocytosis X

### Definitions

- Neoplastic proliferation of Langerhans cells; recurrent *BRAF* V600E and *MAP2K1* mutations has been reported in LCH

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Rare: Accounts for < 1% of all bone tumors
- Age
  - Usually diagnosed during first 3 decades of life; disseminated disease with extraosseous lesions typically occurs in first 2 years of life
- Sex
  - M:F = ~ 2:1

### Site

- Commonly involves skeleton; monostotic more common than polyostotic; other common sites of involvement include skin, lungs, and lymph nodes
- Can develop in any bone but most common in craniofacial bones

### Presentation

- Associated with variety of clinical syndromes that vary due to symptoms and number, site, and size of tumors; localized pain; large tumors may undergo pathologic fracture

### Treatment

- Depends on site and size of lesion, age of patient, and presence or absence of multifocal disease
  - Monostotic disease usually managed by curettage or by direct intralesional injection of corticosteroids
  - Tumors located in difficult sites to access surgically may be treated with low-dose radiation therapy
  - Chemotherapy (including BRAF inhibitors) may be administered in setting of disseminated and fulminant disease

### Prognosis

- Patients with monostotic skeletal involvement have excellent prognosis; usually remain disease free after adequate therapy; multifocal systemic disease has guarded prognosis; *BRAF* mutation may be associated with resistance to conventional therapy

## IMAGING

### Radiographic Findings

- Well-defined lytic lesion; minority of cases have ill-defined and permeative margins, resembling osteomyelitis; sequestrum may be seen
- Discretely punched-out lesions may involve tables of skull unevenly; results in beveled edge appearance
- Cortical involvement may elicit periosteal reaction, which may be more extensive than would be expected from degree of cortical destruction
- Healing is heralded by progressive sclerosis of surrounding bone

### MR Findings

- Hypointense on T1-weighted images; hyperintense on T2-weighted images: Associated marrow and soft tissue edema is better seen

### CT Findings

- Shows bone and soft tissue extent; periosteal reaction is well seen, usually lamellated

### Bone Scan

- Increased uptake; better tool to evaluate multiple lesions

## MACROSCOPIC

### General Features

- Well circumscribed, tan-yellow, soft; 1-5 cm in diameter

## MICROSCOPIC

### Histologic Features

- Proliferating Langerhans cells are ovoid or round, histiocytic cells, 10-15 µm in diameter; arranged in aggregates, sheets, or individually
- Cells have eosinophilic cytoplasm and contain central, ovoid, coffee bean-shaped or deeply indented nuclei that have pale chromatin and inconspicuous nucleoli; coffee bean appearance produced by linear grooves that traverse length of nuclei
- Most Langerhans cells are mononuclear; some cells contain multiple nuclei; mitotic figures: Commonplace; atypical forms: Absent
- Eosinophils present in varying numbers are distributed evenly or arranged in clusters; other types of inflammatory cells, including lymphocytes, plasma cells, macrophages, neutrophils, and osteoclast-type giant cells; necrosis may be seen in minority of cases

### Ultrastructural Features

- Birbeck granules are tubular pentalaminar membrane-bound cytoplasmic organelles; oval protrusions

## ANCILLARY TESTS

### Immunohistochemistry

- Langerhans cells express CD1a, S100 protein, and langerin

## DIFFERENTIAL DIAGNOSIS

### Acute and Chronic Osteomyelitis/Skeletal Diseases With Increased Eosinophils

- Acute osteomyelitis typically has prominent neutrophilic and fibrinous exudate in addition to bone necrosis
- Chronic osteomyelitis exhibits mixed inflammatory infiltrate that may contain histiocytes that lack characteristic features of Langerhans cells

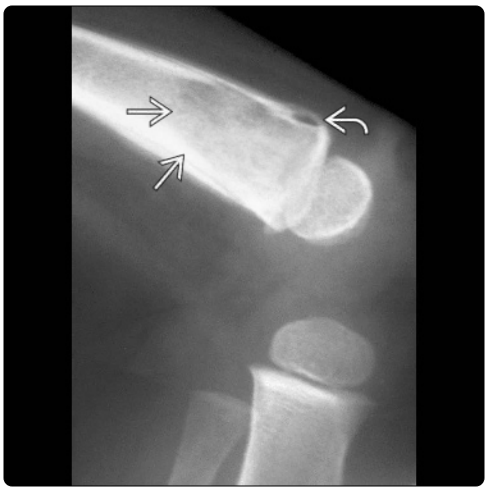
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1. Zeng K et al: BRAFV600E and MAP2K1 mutations in Langerhans cell histiocytosis occur predominantly in children. Hematol Oncol. ePub, 2016

**Triangular Lytic Lesion**



**Ill-Defined Lesion**



**(Left)** *Radiograph from a child with Langerhans cell histiocytosis shows a triangular lytic lesion involving the distal femoral metaphysis extending to the open growth plate with thinning of the lateral cortex. The lesion is well demarcated medially.* **(Right)** *Lateral view radiograph of the knee shows a lesion with ill-defined borders involving the distal femur with lucencies in the anterior cortex. The lesion extends to the open growth plate and into the distal diaphysis.*

**Lytic Lesion of Mandible**



**Pathologic Fracture of Rib**

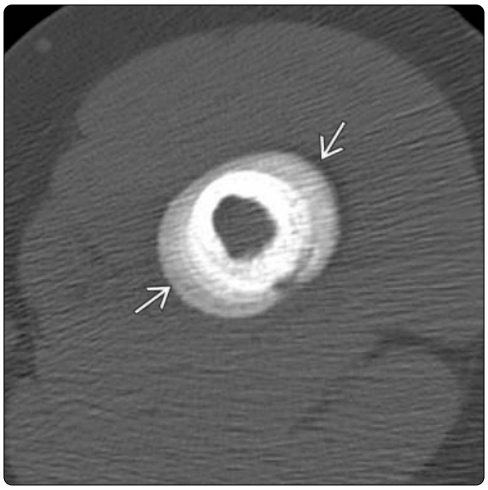


**(Left)** *Axial CT of Langerhans cell histiocytosis shows a lytic lesion in the right mandible with cortical destruction anteriorly and thinning posteriorly. The last tooth on the right is nearly "floating."* **(Right)** *Axial CT scan of Langerhans cell histiocytosis shows a lytic lesion in an upper thoracic rib posteriorly. The lesion has caused a pathologic fracture, and the posterior cortex is expanded and confined by a thin periosteal shell.*

**Ill-Defined Lesion**



**Florid Periosteal Bone Formation**

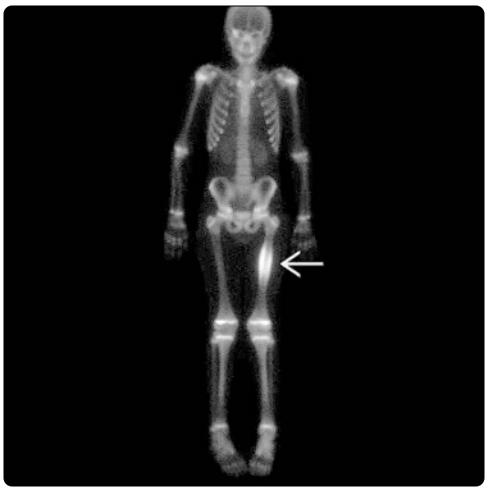


**(Left)** *Plain radiograph in a patient with Langerhans cell histiocytosis demonstrates an intramedullary lucency involving the midshaft of the femur with some medial periosteal reaction.* **(Right)** *Axial CT scan of the femur in a patient with Langerhans cell histiocytosis shows an intramedullary lesion with intact cortex and dense, thick periosteal new bone formation mimicking an aggressive tumor, such as Ewing sarcoma. Small cortical tunnels are seen.*

Hyperintense Lesion

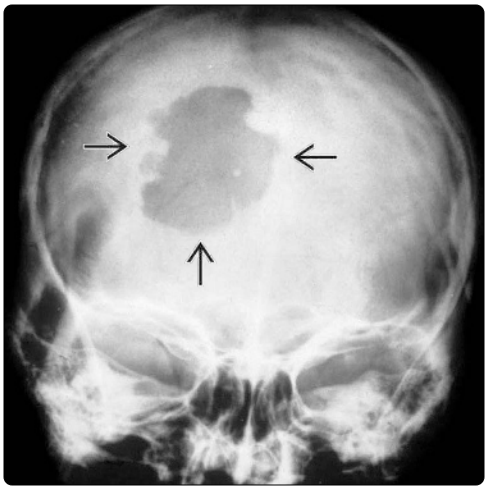


Hot Lesion

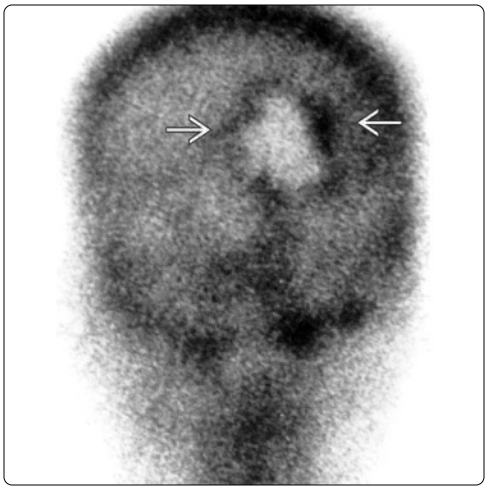


**(Left)** *Sagittal fluid-sensitive MR of Langerhans cell histiocytosis involving the femur shows diffuse hyperintense signal in the mid femoral shaft representing marked marrow edema. Edema and inflammation are also seen in the anterior and posterior soft tissues.* **(Right)** *Whole-body Tc-99m scan shows increased uptake of the radionuclide in the midshaft of the left femur. Dense uptake is seen along the medial and lateral cortices from the periosteal new bone formation.*

Lytic Lesion Involving Skull

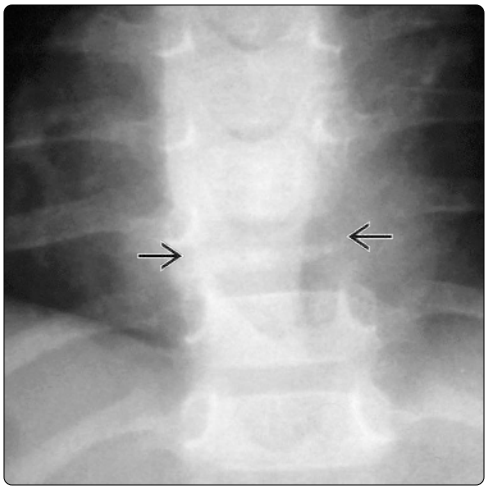


Cold Lesion

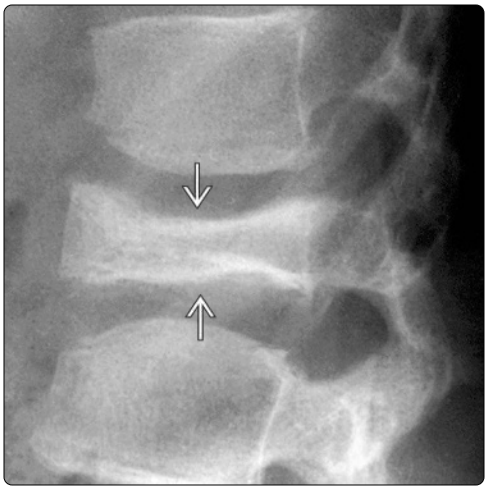


**(Left)** *Langerhans cell histiocytosis involving the craniofacial skeleton demonstrates a well-demarcated geographic lesion in the skull. The increased density in the surrounding bone represents reactive changes.* **(Right)** *Radionucleotide bone scan in a patient with Langerhans cell histiocytosis shows a geographic lesion involving the skull with increased uptake along the margins. The lesion itself shows decreased uptake, something that can be seen in this disease.*

Radiograph of Vertebra Plana

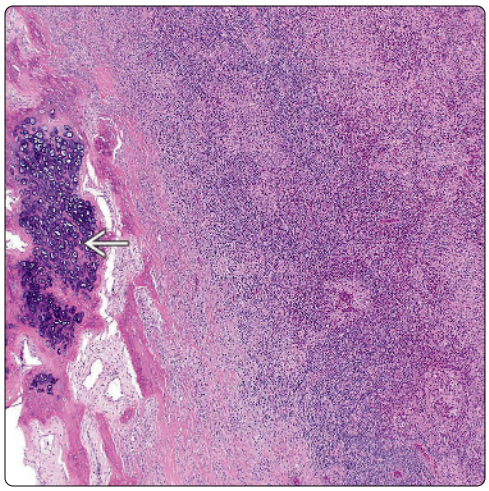


Collapsed Vertebra (Vertebra Plana)

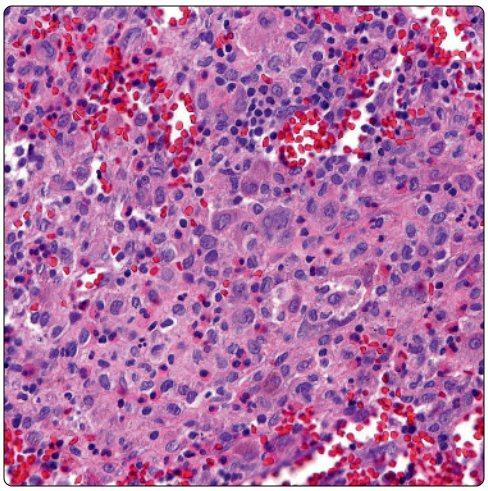


**(Left)** *Radiograph of the lower thoracic spine in a patient with Langerhans cell histiocytosis shows the typical vertebra plana deformity of one of the vertebral bodies.* **(Right)** *Lateral view radiograph shows a collapsed vertebral body (vertebra plana) in the lower thoracic spine. This is a typical finding in Langerhans cell histiocytosis involving the vertebrae. The involved vertebra is ~ 1/2 the height of the adjacent proximal and distal vertebrae.*

### Pathologic Fracture

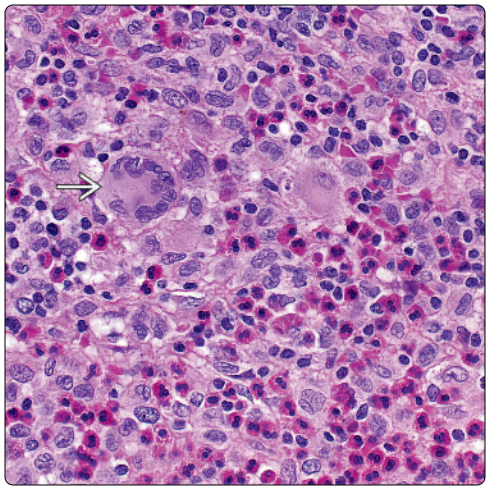


### Diffuse Proliferation of Neoplastic Cells

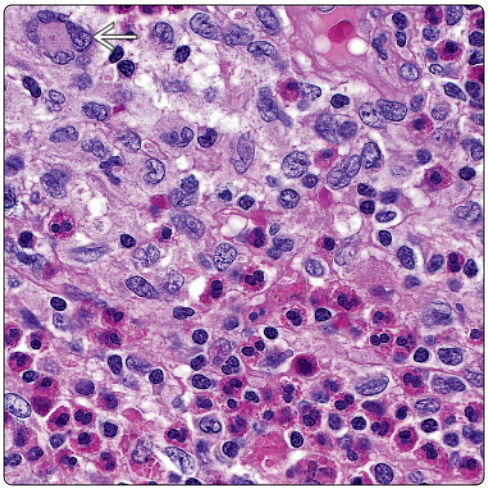


**(Left)** *In this example of Langerhans cell histiocytosis arising in a rib, the neoplastic cells demonstrate a diffuse growth pattern and have replaced the marrow cavity. The cellular fibrocartilaginous tissue represents a fracture callus* ⇨. **(Right)** *In this medium-power view of Langerhans cell histiocytosis, there is diffuse proliferation of the mononuclear cells with granular eosinophilic cytoplasm that are admixed with scattered eosinophils and areas of hemorrhage.*

### Mono- and Multinucleated Cells

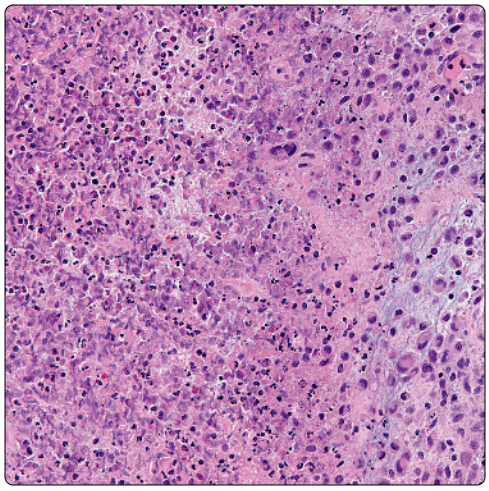


### Mononuclear Cells With Cleaved Nuclei

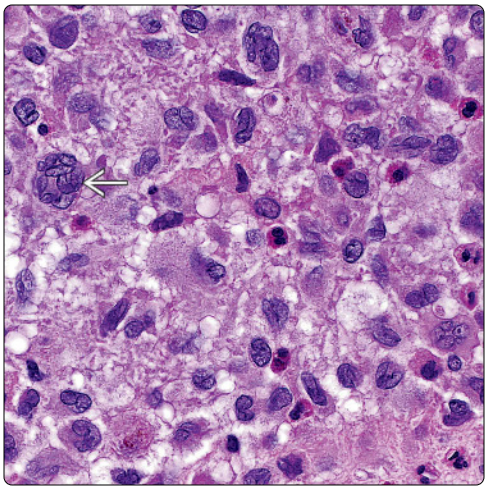


**(Left)** *Langerhans cell histiocytosis of bone shows an admixture of mononuclear cells, multinucleated giant cells, and eosinophils. The mononuclear cells have eosinophilic cytoplasm and irregular nuclei. The multinucleated giant cells* ⇨ *have peripheral arrangement of the nuclei that are similar in appearance to those of the mononuclear cells.* **(Right)** *Higher power view of Langerhans cell histiocytosis with multinucleated giant cells shows the irregular nuclei of the mononuclear cells and giant cells* ⇨.

### Area of Necrosis

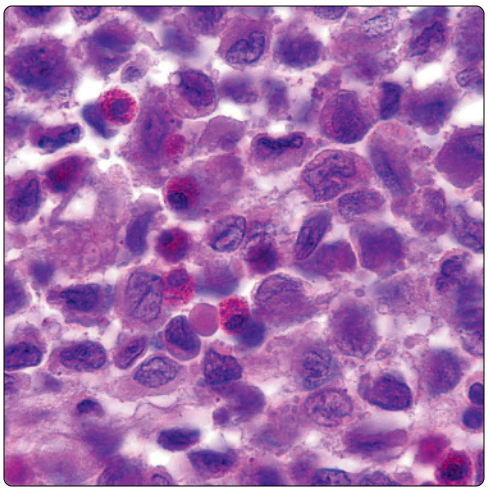


### Mononuclear and Multinucleated Cells

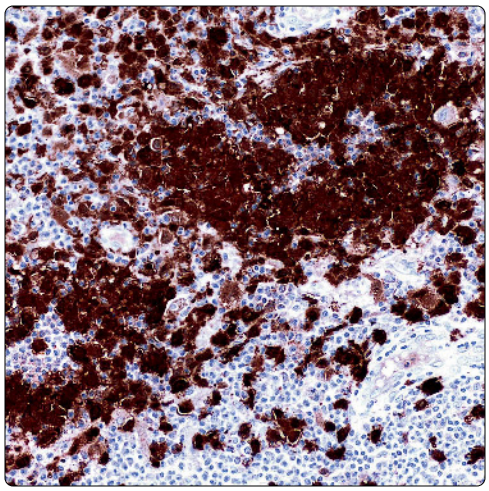


**(Left)** *Langerhans cell histiocytosis shows an area of necrosis. This is rarely seen in Langerhans cell histiocytosis and should not be misinterpreted as a malignant neoplasm.* **(Right)** *High-power view of Langerhans cell histiocytosis shows an admixture of mononuclear cells and giant cells. The mononuclear cells have granular eosinophilic cytoplasm and irregular-shaped nuclei. The giant cells* ⇨ *have peripheral arrangement of the nuclei that are similar to the nuclei in the mononuclear cells.*

**Coffee Bean-Shaped Nuclei**

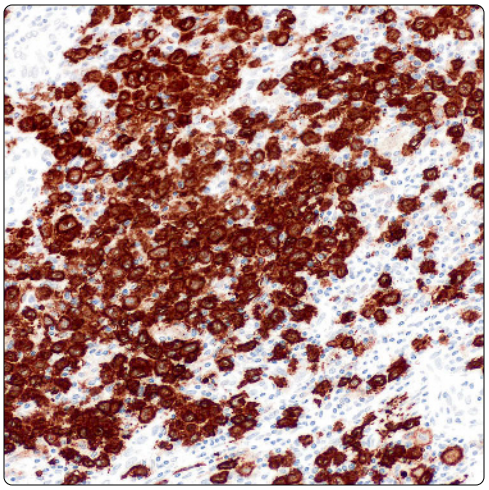


**S100 Immunohistochemical Stain**

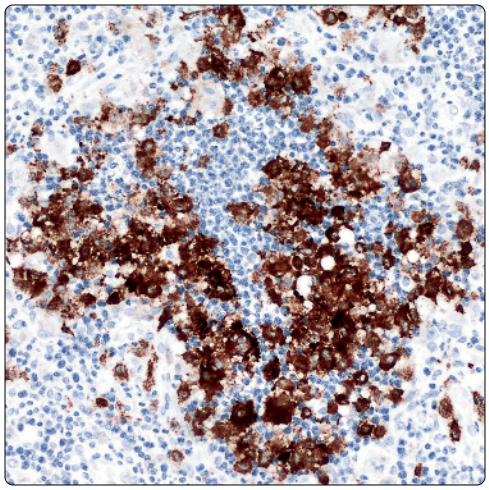


**(Left)** *Very high-power view of Langerhans cell histiocytosis shows that the neoplastic cells have eosinophilic cytoplasm and large, cleaved (coffee bean-shaped) nuclei. Also note the scattered eosinophils in the background.* **(Right)** *Langerhans cell histiocytosis stained immunohistochemically for S100 protein shows diffuse strong staining for this antibody. This is typically seen in Langerhans cell histiocytosis.*

**CD1 Immunohistochemical Stain**



**Langerin Immunohistochemical Stain**

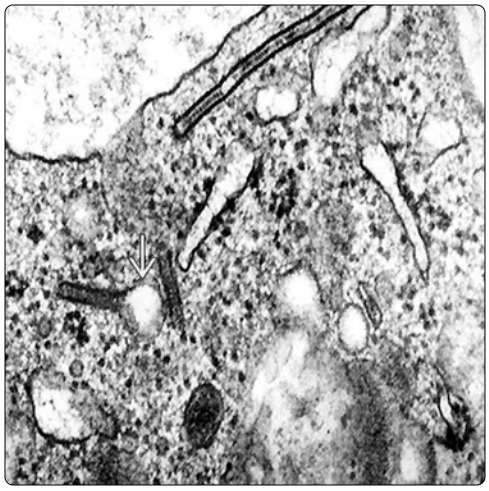


**(Left)** *Immunohistochemical stain for CD1a demonstrates that the mononuclear cells in Langerhans cell histiocytosis show diffuse strong staining for this antibody.* **(Right)** *Langerhans cell histiocytosis stained immunohistochemically for langerin shows that the neoplastic cells stain diffusely and strongly for this antibody. Langerin is a very specific and sensitive stain for Langerhans cell histiocytosis.*

**Birbeck Granule**



**Tennis Racket Birbeck Granules**



**(Left)** *Electron micrograph of a mononuclear cell in Langerhans cell histiocytosis shows the typical ultrastructural features. The nucleus is cleaved ⇨, there is abundant cytoplasm, and scattered Birbeck granules are present ⇨, some of which have the appearance of a tennis racket ⇨.* **(Right)** *Electron micrograph shows the typical features of the Birbeck granules. They are pentalaminar and frequently have a bulbous end, mimicking a tennis racket ➡.*

# Primary Lymphoma

KEY FACTS

## TERMINOLOGY

- Primary lymphoma of bone is defined as lymphoma originating in bone ± extension into adjacent soft tissues

## ETIOLOGY/PATHOGENESIS

- Most primary bone lymphomas are sporadic and of unknown etiology

## CLINICAL ISSUES

- Usually adults; ~ 50% are > 40 years
- Femur is most common location followed by pelvis, vertebrae, and humerus
- ~ 10-40% of cases of lymphoma are multifocal/polyostotic; several lesions in 1 bone or multiple bones involved concurrently
- Produces pain, erythema, swelling
- Treatment with radiation and chemotherapy of large B-cell lymphoma has 75% 10-year survival

## IMAGING

- Large, lytic, and destructive
- In some cases, tumor may elicit extensive medullary sclerosis

## MICROSCOPIC

- Diffuse large B-cell lymphoma is most common type by far in both adults and children
- Lymphoblastic lymphoma is 2nd most common type to arise in children (40% of cases); uncommon in adults
- Anaplastic large cell lymphoma is rare but most common primary T-cell lymphoma of bone

## ANCILLARY TESTS

- Immunoprofile varies according to type

## TOP DIFFERENTIAL DIAGNOSES

- Osteomyelitis, Langerhans cell histiocytosis, Ewing sarcoma, metastatic small cell carcinoma, neuroblastoma, rhabdomyosarcoma, other round cell malignancies

**Subtle Lytic Lesion**

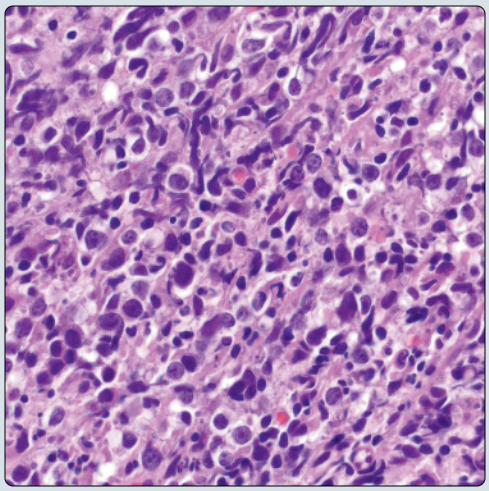


**Permeative Mass**

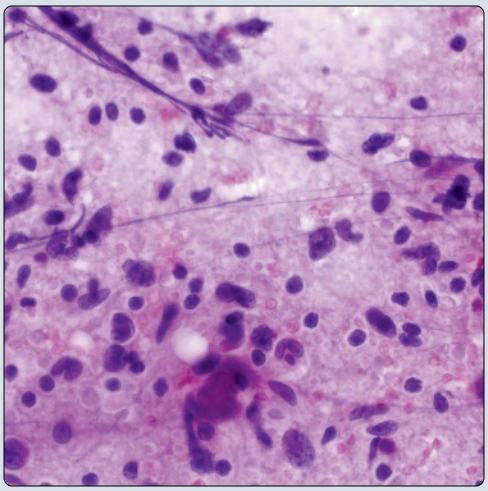


**(Left)** *This large B-cell lymphoma presented on the radiograph as a subtle, poorly defined radiolucency involving the femoral head, neck, and greater trochanter. There is no periosteal reaction.* **(Right)** *A large B-cell lymphoma permeates the marrow space as a tan-yellow lesion. In an area, it transgresses the cortex inferior to the greater trochanter and infiltrates the skeletal muscle.*

**Large Cells in Sheets**



**Touch Prep of Large B-Cell Lymphoma**



**(Left)** *The tumor is composed of sheets of noncohesive large cells that have an increased nuclear:cytoplasmic ratio, nuclei that range from round to irregular, and small amounts of eosinophilic cytoplasm. Immunohistochemistry documents that the large cells are B cells.* **(Right)** *In this touch preparation of a large B cell lymphoma, the tumor cells can be seen to have large hyperlobated and elongate nuclei. Scattered small lymphocytes are in the background.*

## TERMINOLOGY

### Synonyms

- Reticulum cell sarcoma (outdated)

### Definitions

- Malignant lymphoid neoplasm producing at least 1 mass within bone without involvement of extraregional lymph nodes and extranodal sites
  - No extraosseous distant disease should be identified within 4-6 months of initial diagnosis

## ETIOLOGY/PATHOGENESIS

### Etiology

- Sporadic and of unknown etiology
- Rarely reported in patients with HIV, longstanding osteomyelitis, or Paget disease of bone

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Rare; accounts for 5% of primary malignant bone tumors and 5% of extranodal lymphomas
    - < 1% of all lymphomas arise in bone; incidence in children is 2-9%
- Age
  - Usually adults; 5th-6th decades, 50% are > 40 years; minority in children and adolescents
- Sex
  - Male predominance 1.6:1

### Site

- Located in femur followed by pelvis, vertebrae, and humerus
- Usually arises in metadiaphyseal region
- Multifocal (polyostotic) in 10-40% of cases; several lesions in 1 bone or involving multiple bones concurrently

### Presentation

- Pain, erythema, swelling, pathological fracture
- Tumors of axial skeleton may cause neurological symptoms
- 10% of patients have constitutional symptoms: Fever, anemia, fatigue
  - More common with polyostotic disease

### Treatment

- Radiation and chemotherapy; surgery for fracture

### Prognosis

- 10-year survival for large B-cell lymphoma: 75%
- Follicular center tumors have better prognosis
- Outcome for anaplastic large cell lymphoma is poor

## IMAGING

### Radiographic Findings

- Large, lytic, destructive; moth-eaten or permeative margins
- Erodes cortex, soft tissue mass, and periosteal reaction
  - Soft tissue mass tends to be concentric around bone
- May elicit extensive medullary sclerosis
- Findings may be minimal on x-ray with changes only on bone scan, CT, or MR

### MR Findings

- Signal intensity similar to muscle on T1 and heterogeneous on T2
  - Best to demonstrate soft tissue component

### CT Findings

- Lytic or sclerotic mass

## MACROSCOPIC

### General Features

- Replaces medullary cavity, erodes cortex, involves soft tissue
- Moderately firm, gray-white, fleshy with necrosis

## MICROSCOPIC

### Histologic Features

- Morphology same as nodal lymphoma
- Diffuse large B-cell lymphoma most common in adults and children
  - Lymphoblastic lymphoma 2nd most common in children (40% of cases)
- Anaplastic large cell lymphoma rare; most common T-cell lymphoma of bone
- Other lymphomas rarely arise in bone
- Extensive necrosis or crush artifact common

## ANCILLARY TESTS

### Immunohistochemistry

- Immunoprofile varies according to type
- Large B-cell lymphomas express B-cell markers
- Anaplastic large cell lymphoma positive or negative for ALK
  - ALK(+) tumors mainly affect children, whereas ALK(-) tumors affect adults
- Lymphoblastic lymphoma may be LCA(-) and CD99(+)

## DIFFERENTIAL DIAGNOSIS

### Round Cell Lesions

- Osteomyelitis, Langerhans cell histiocytosis, Ewing sarcoma, metastatic small cell carcinoma, neuroblastoma, rhabdomyosarcoma, other round cell malignancies
- Immunohistochemistry and cytogenetics may be necessary

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Think lymphoma if malignant round cell tumor with extensive necrosis or crush artifact

## SELECTED REFERENCES


1. Chisholm KM et al: Primary lymphoma of bone in the pediatric and young adult population. Hum Pathol. ePub, 2016
2. Murphey MD et al: Primary musculoskeletal lymphoma. Radiol Clin North Am. 54(4):785-95, 2016
3. Wu H et al: Prognostic significance of soft tissue extension, international prognostic index, and multifocality in primary bone lymphoma: a single institutional experience. Br J Haematol. 166(1):60-8, 2014
4. Demircay E et al: Malignant lymphoma of bone: a review of 119 patients. Clin Orthop Relat Res. 471(8):2684-90, 2013

### Ill-Defined Area of Sclerosis



### Subtle Lytic Lesion

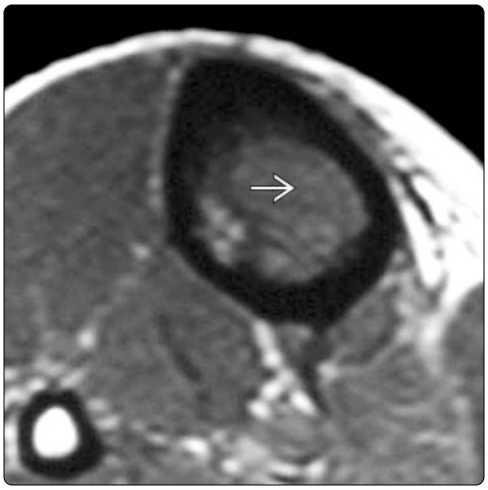


**(Left)** *Radiograph shows lymphoma of bone manifesting as an ill-defined zone of medullary sclerosis. The cortex is intact with no identifiable periosteal reaction.* **(Right)** *Radiograph shows lymphoma of bone of the proximal tibial metaphysis appearing as a poorly defined lytic lesion with endosteal resorption anteriorly and posteriorly. The distal component is indistinct with an area of sclerosis. The cortex and periosteum are intact, and there is no soft tissue component.*

### Marrow Replacing Tumor



### Intramedullary Tumor



**(Left)** *Fluid-sensitive coronal MR with fat saturation shows that the bone lymphoma replaces the marrow of the proximal tibial diaphysis. The small hyperintense soft tissue component with intact-appearing cortex is a manifestation of the permeative nature of the lesion.* **(Right)** *Axial T1WI MR shows a lymphoma that has a hypointense signal within the medullary cavity of the tibia. The tumor appears to be confined to the bone, and the cortex seems to be intact.*

### Poorly Defined Lesion

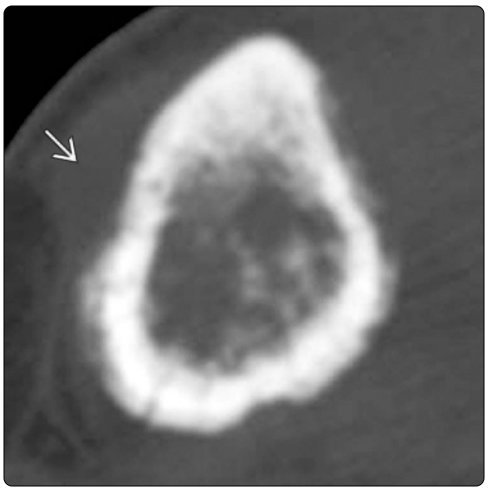


### Extension Into Soft Tissues

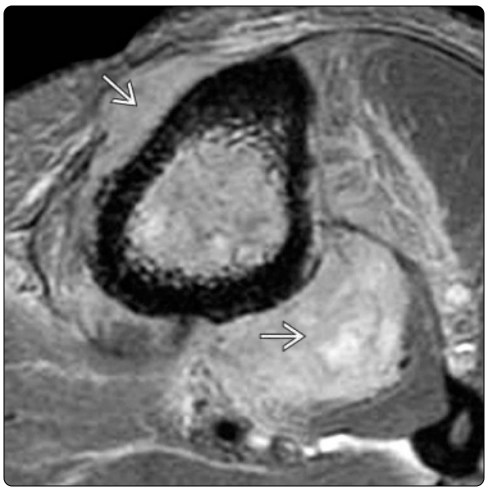


**(Left)** *This lymphoma of bone presents as an ill-defined, permeative lesion in the tibia. The tumor produces subtle lytic change and has indistinct margins. Note the circumferential periosteal reaction that produces cortical thickening.* **(Right)** *Coronal T2WI fat-saturated MR shows lymphoma of the tibia that extends into the soft tissues with a heterogeneous signal intensity. Most of the tumor is hyperintense, and it has a well-demarcated proximal margin.*

### Erosion of Bone



### Soft Tissue Extension

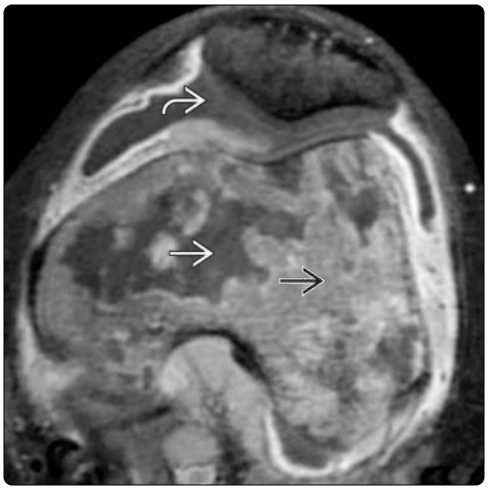


**(Left)** *Axial CT scan shows lymphoma of the proximal tibia appearing as a mixed lucent and sclerotic lesion that involves the cortex and elicits periosteal new bone formation. A soft tissue mass is seen anteromedially.* **(Right)** *Axial T1WI fat-saturated MR following intravenous gadolinium shows a minimally enhancing lesion replacing the marrow that has a soft tissue mass anteromedially and posterolaterally. The mass is hyperintense in comparison to the muscles.*

### Subtle Lysis of Bone



### Geographic Marrow Involvement



**(Left)** *Radiograph shows an ill-defined area of destruction caused by lymphoma in the femur. It is most evident laterally where there is cortical penetration and fullness of the lateral soft tissues.* **(Right)** *Axial T1WI fat-saturated MR following intravenous gadolinium shows a heterogeneously enhancing lymphoma. The scattered nonenhancing areas likely represent tumor necrosis. Note the nonenhancing joint effusion anteriorly with enhancing synovial rim.*

### Medullary Area of Lysis

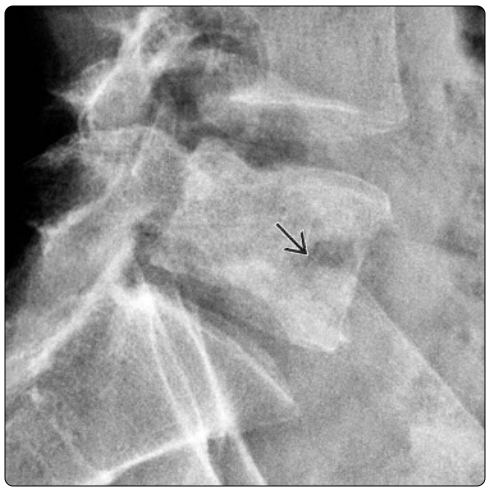


### Marrow Replacement



**(Left)** *Radiograph of an intramedullary lytic lymphoblastic lymphoma produces endosteal resorption in the distal humeral diaphysis. The margins of the tumor are indistinct, and the outer cortex appears intact with no periosteal reaction or soft tissue extension.* **(Right)** *Sagittal T2WI fat-saturated MR of lymphoblastic lymphoma shows that the tumor is hypointense and involves most of the distal 1/2 of the humerus. The adjacent marrow is hyperintense.*

**Mixed Lytic and Sclerotic Lesion**



**Extension Into Soft Tissue**

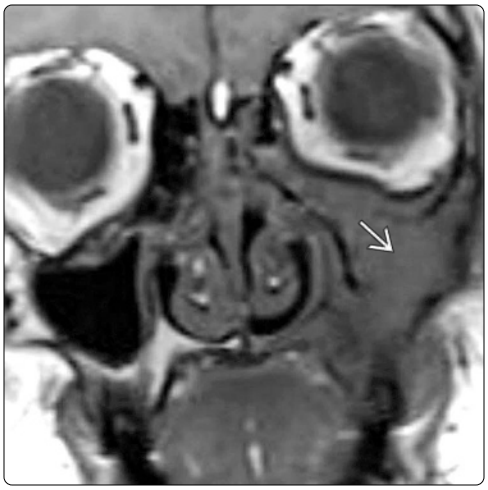


**(Left)** *Radiograph of a lymphoma of the L5 vertebra shows a mixed lucent ⇨ and sclerotic lesion. The tumor is confined to the bone, and there is no cortical destruction or periosteal reaction.* **(Right)** *Sagittal T1WI MR shows a primary bone lymphoma that replaces the marrow of the L5 vertebral body and the spinous process and adjacent soft tissues ⇨. The tumor causes mild endplate and disc compression posteriorly and extends into the spinal canal ⇨ compressing the cord.*

**Destructive Mass**



**Tumor Filling Sinus**

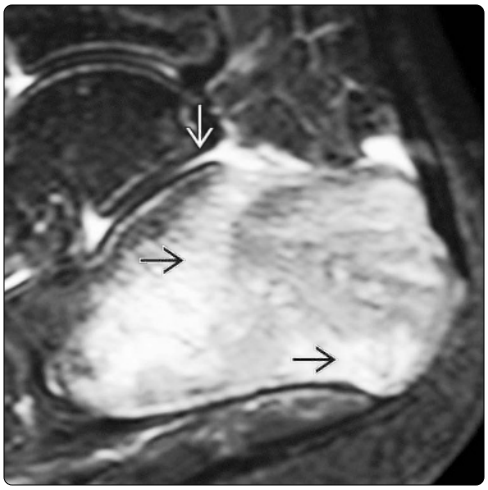


**(Left)** *Axial CT shows a diffuse large B-cell lymphoma of the maxilla and ethmoid bones ⇨ causing permeative lytic and sclerotic destruction of the left orbital floor and extending into the adjacent sinuses. The tumor focally destroys the cortex anteriorly ⇨.* **(Right)** *Coronal T1WI MR sequence of a large B-cell lymphoma of the maxilla and ethmoid shows a hypointense-signal-intensity mass ⇨ in the left maxillary sinus. The superior and inferolateral walls of the sinus are destroyed.*

**Areas of Dense Sclerosis**

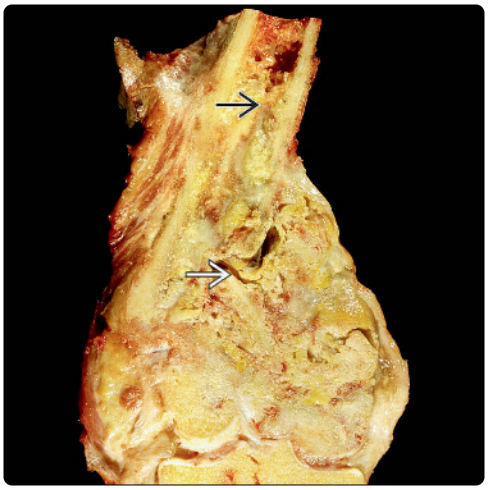


**Replacement of Marrow Fat**

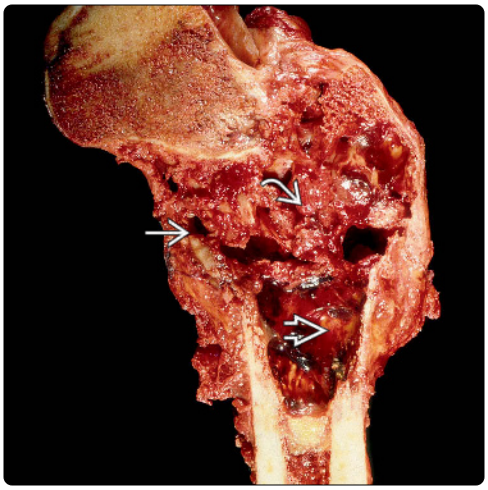


**(Left)** *A lymphoma of the posterior calcaneus shows an ill-defined lytic lesion ⇨ with dense sclerosis ⇨ superiorly and distally. There is slight cortical thickening of the plantar cortex ⇨ and the subtalar joint is intact.* **(Right)** *Sagittal T2WI fat-saturated MR of lymphoma shows a heterogeneously hyperintense mass ⇨ in the posterior calcaneus producing significant hyperintensity in the superior and distal areas. An effusion is present in the subtalar joint ⇨.*

### Large, Tan-Yellow Mass

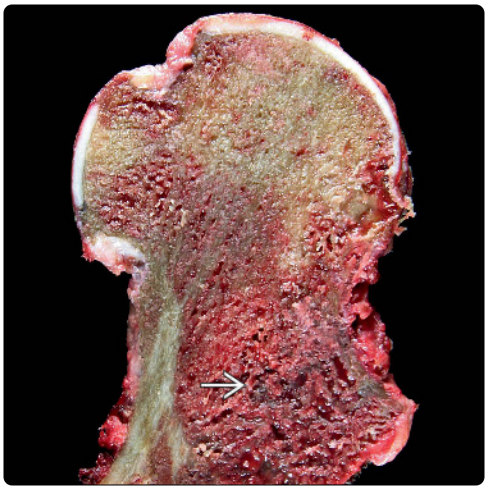


### Hemorrhagic Mass With Fracture

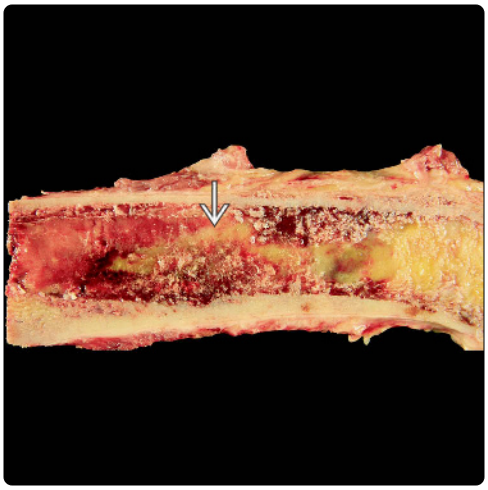


**(Left)** *A diffuse large B-cell lymphoma destroying the distal femur has caused a displaced pathologic fracture. The tan-yellow mass replaces the metaphysis, epiphysis, and proximal medullary canal.* **(Right)** *A destructive diffuse large B-cell lymphoma of the femur has resulted in a pathologic fracture. The hemorrhagic tan tumor has caused resorption of the cortex and fills the medullary cavity. The femoral head contains hematopoietic and fatty marrow.*

### Infiltrative Tumor

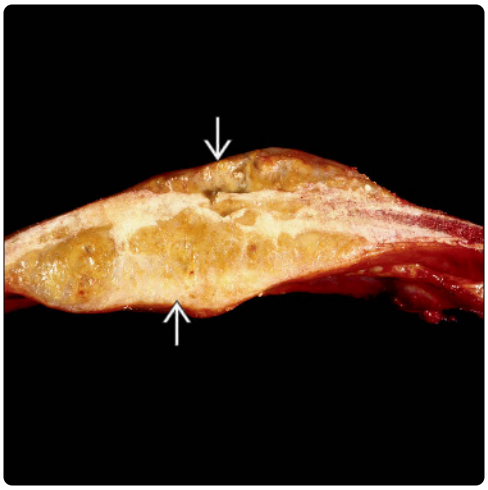


### Necrotic Tumor



**(Left)** *A resected proximal femur contains a primary high-grade follicular B-cell lymphoma of bone that is located in the base of the femoral neck. The tumor is soft and red and permeates the marrow spaces but does not involve the cortex.* **(Right)** *A resected segment of femur harbors a treated diffuse large B-cell lymphoma of bone. The tumor is completely necrotic and fills the medullary cavity of the diaphysis. The cortex is intact, and there is no periosteal reaction.*

### Cortical Destruction

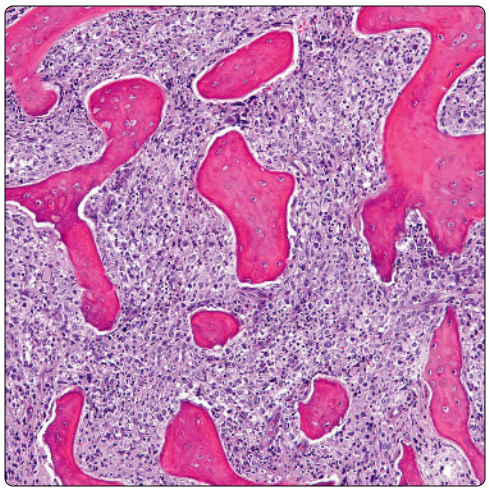


### Treated Tumor

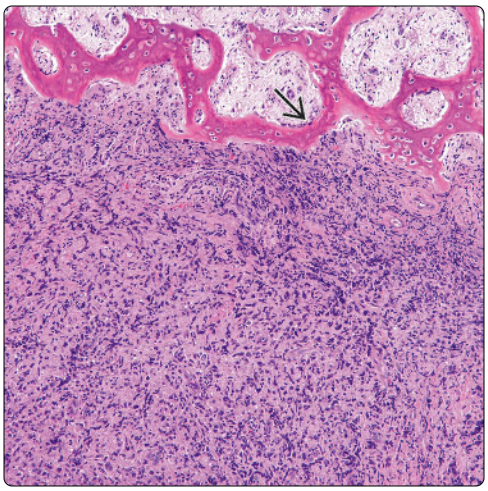


**(Left)** *Primary nodular sclerosis type of Hodgkin disease of the rib presents as a destructive, tan-yellow mass. The tumor fills the medullary cavity and extends into the soft tissues on both sides of the bone.* **(Right)** *A treated B-cell lymphoblastic lymphoma of bone is shown occupying the medullary cavity of the distal diaphysis of the humerus. The tan-white tumor does not involve the cortex, and the periosteum and adjacent skeletal muscle are intact.*

**Infiltrative Growth**

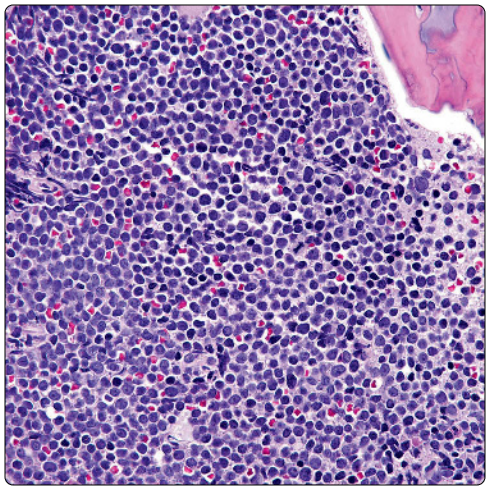


**Well Demarcated**

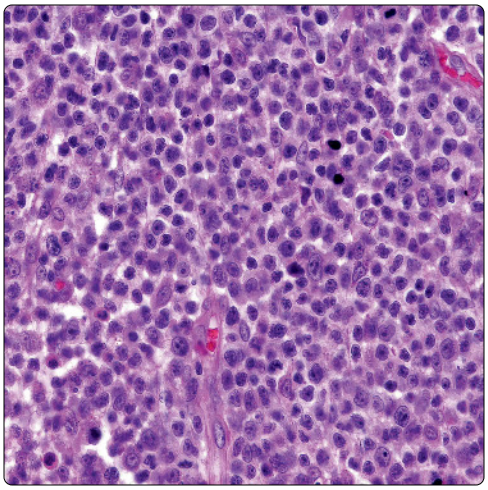


**(Left)** *Diffuse large B-cell lymphoma of bone replaces the marrow elements and encases bony trabeculae, some of which consists of woven bone. This type of infiltrative growth pattern is characteristic of lymphoma of bone.* **(Right)** *Diffuse large B-cell lymphoma of bone with subtle sclerotic stroma abuts a zone of reactive woven bone with osteoblastic rimming ⇨. An unusual feature of the growth pattern is that the tumor is well demarcated from the adjacent bone.*

**Sheets of Round Cells**

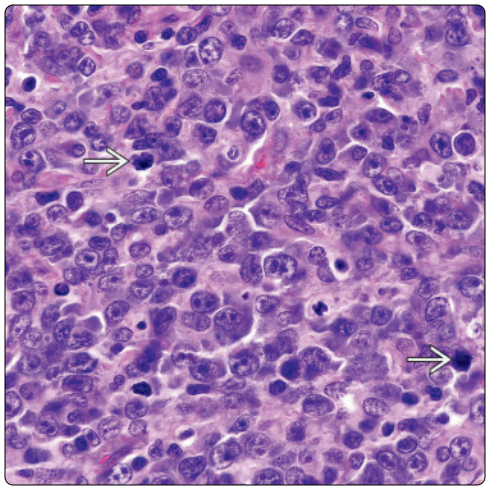


**Irregular Nuclear Contours**

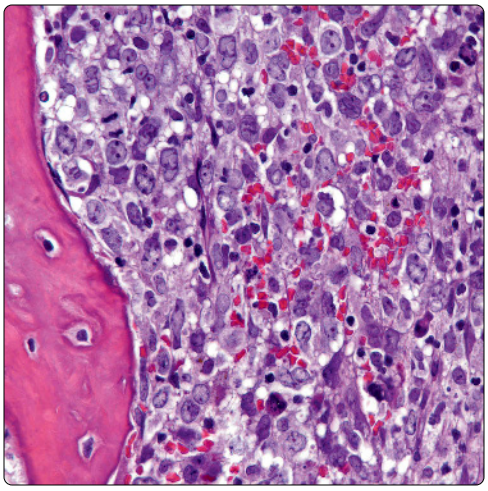


**(Left)** *Lymphoblastic B-cell lymphoma replaces the marrow and is adjacent to a bony trabecula. The tumor cells grow in a sheet-like pattern and are uniform in size and shape with round nuclei.* **(Right)** *Diffuse large B-cell lymphoma fills the marrow cavity and replaces the preexisting elements. The dyscohesive tumor cells have a small to moderate amount of cytoplasm, and the nuclei have fine chromatin, visible nucleoli, and irregular nuclear contours. Mitoses are few in number.*

**Prominent Nucleoli**

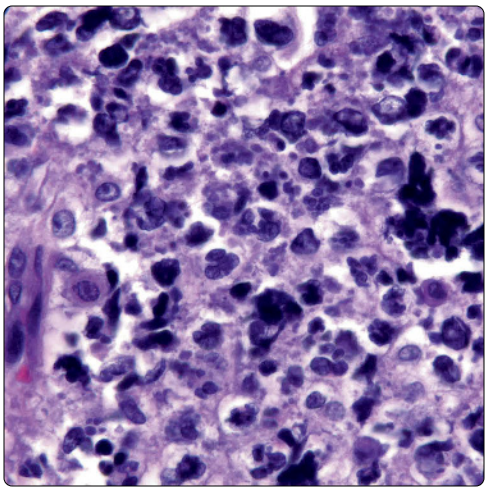


**Reactive Woven Bone**

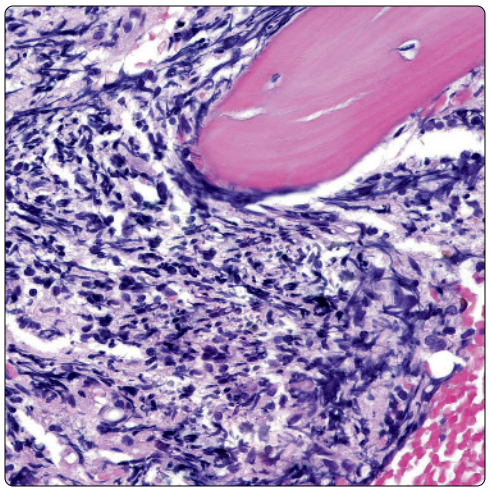


**(Left)** *High-power view shows diffuse large B-cell lymphoma composed of cells that are ~ the size of macrophages. The tumor cells have pink cytoplasm and large vesicular nuclei with prominent nucleoli. Scattered apoptotic cells ➡ are present throughout the tumor.* **(Right)** *Diffuse large B-cell lymphoma is shown replacing the marrow adjacent to a woven bone trabecula. This type of bone can produce the sclerosis that may be present on imaging studies of this type of tumor.*

### Multilobated Nuclei

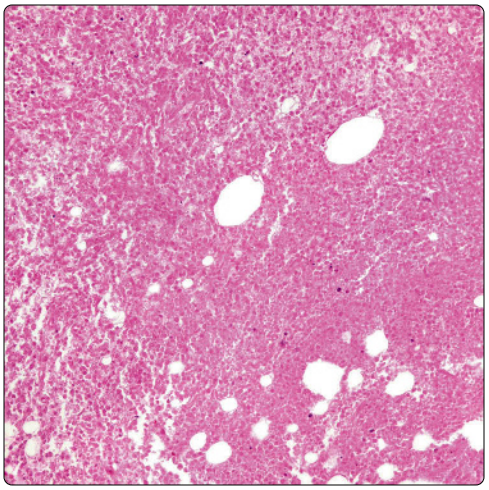


### Smear Artifact

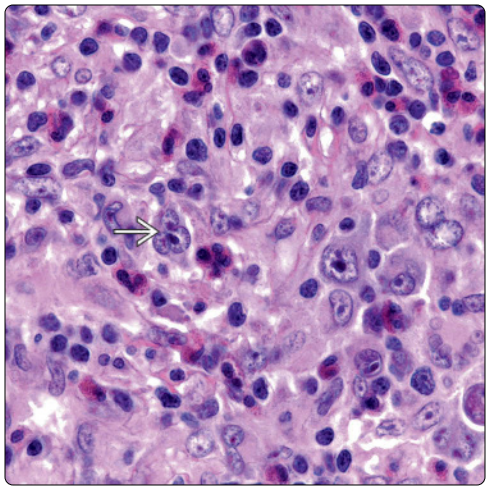


**(Left)** *Large cell lymphoma of bone composed of pleomorphic cells is shown. The cells are multilobated and hyperchromatic with irregular nuclear contours. Many of the tumor cells have a moderate amount of eosinophilic cytoplasm.* **(Right)** *Large cell lymphoma of bone demonstrates crush artifact that can prevent definitive diagnosis. This type of change is a common problem associated with bone lymphoma biopsies. Other tumors with this problem include Ewing sarcoma.*

### Ghost Cells

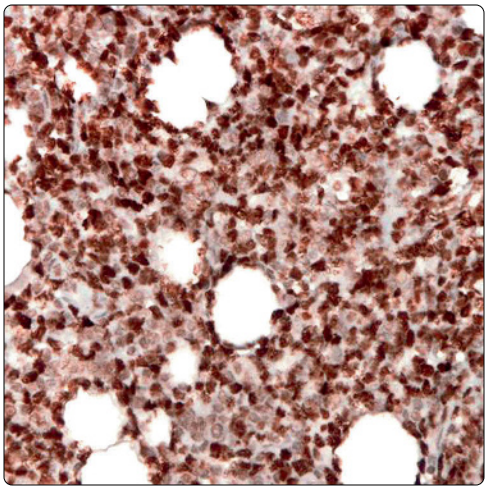


### Reed-Sternberg Cells

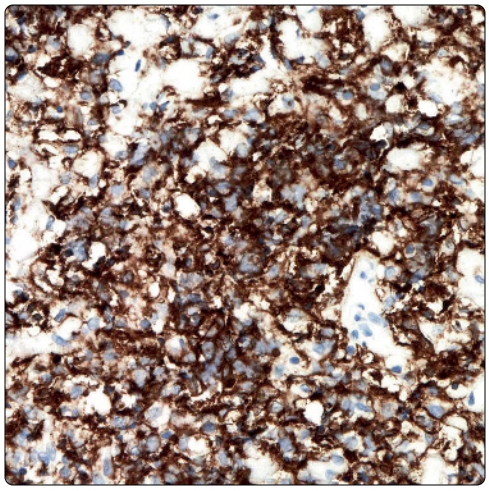


**(Left)** *Diffuse large B-cell lymphoma shows complete necrosis of the tumor cells. Extensive necrosis can be seen in treated tumors, as in this particular case, but can also be seen in biopsies of untreated lymphomas, making definitive diagnosis difficult.* **(Right)** *Hodgkin lymphoma of bone contains characteristic Reed-Sternberg cells ➡ that are bilobate and have large dark eosinophilic nucleoli. The accompanying mixed inflammatory infiltrate is rich in eosinophils.*

### Strong Nuclear Staining



### Membranous Staining



**(Left)** *Lymphoblastic lymphoma of bone replaces the marrow. Nuclei stain strongly for TdT, which is expressed in this type of hematopoietic malignancy. This type of tumor may not stain with LCA, but expresses CD99, which can cause confusion with Ewing sarcoma.* **(Right)** *Diffuse large B-cell lymphoma with strong membranous expression of CD20 is shown. This immunoprofile excludes other malignant round cell tumors.*

# Plasma Cell Myeloma

KEY FACTS

## TERMINOLOGY

- Plasma cell myeloma (PCM) is bone marrow-based, multifocal plasma cell neoplasm associated with M protein in serum &/or urine
- Solitary plasmacytoma of bone is localized bone tumor consisting of monoclonal plasma cells

## CLINICAL ISSUES

- Most common primary malignant bone tumor
- Median age at diagnosis: ~ 70 years
- Most common sites are vertebrae, ribs, skull, pelvis, femur, clavicle, and scapula

## IMAGING

- Well-circumscribed geographic lytic lesion centered in bone marrow without identifiable matrix
- May show multiloculated appearance

## MICROSCOPIC

- Tumoral mass of plasma cells displacing normal bone marrow elements
- Mature plasma cells, plasmablasts, and pleomorphic forms may be seen
- Cytoplasmic immunoglobulin may produce variety of morphologically distinctive findings, including Mott cells and crystalline rods

## ANCILLARY TESTS

- Immunohistochemistry &/or in situ hybridization for light chains assist in recognizing monoclonal plasma cell population

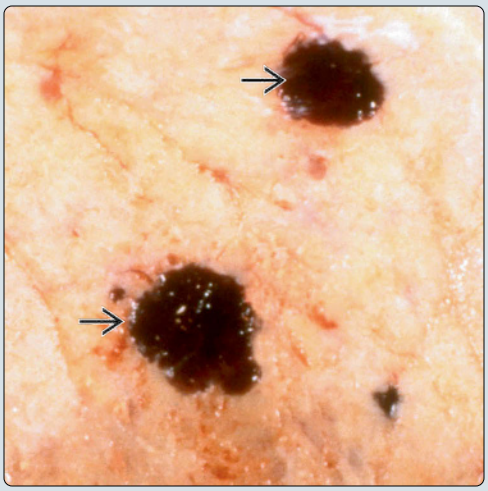
## TOP DIFFERENTIAL DIAGNOSES

- Metastatic carcinoma and lymphoma

### Multiple Round Radiolucencies

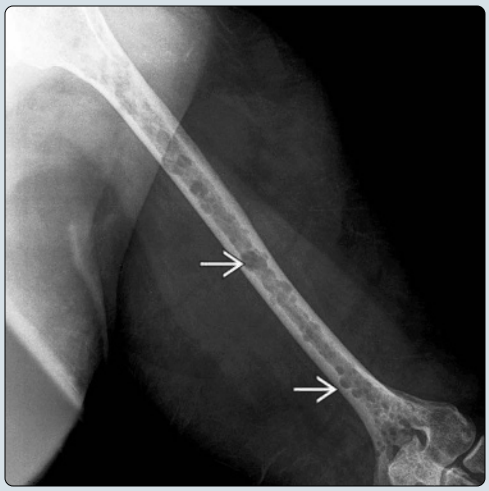


### Dark Red Soft Masses



**(Left)** *Lateral radiograph of skull shows multiple lytic lesions. Note the small punched-out foci of lucency in the frontal and parietal areas. This is a characteristic appearance of plasma cell myeloma.* **(Right)** *Gross image of the skull from a patient with plasma cell myeloma shows 2 punched-out lesions ⇨. Both lesions are soft and hemorrhagic. The bone between the 2 lesions is free of plasma cell myeloma.*

### Many Lytic Lesions



### Poorly Defined Lytic Tumor



**(Left)** *Plain film of humerus demonstrates numerous lytic lesions ⇨ in an individual with plasma cell myeloma. The humerus is studded with punched-out lytic lesions. The sharp margins are characteristic.* **(Right)** *Humerus displays a large focus of lysis ⇨ with erosion of the cortex ⇨. The differential diagnosis includes plasmacytoma, lymphoma, and osteomyelitis. The biopsy revealed plasmacytoma.*

## TERMINOLOGY

### Abbreviations

- Plasma cell myeloma (PCM)

### Definitions

- PCM is bone marrow-based multifocal proliferation of plasma cells associated with M protein in serum &/or urine and evidence of organ damage related to plasma cell neoplasm
  - Bone marrow is site of origin of nearly all plasma cell neoplasms
  - Disease encompasses wide clinical spectrum from asymptomatic to highly aggressive
- Solitary plasmacytoma: Single localized tumor consisting of monoclonal plasma cells
  - No clinical features of PCM
  - No radiographic evidence of additional plasma cell tumors
- Diagnosis of PCM and solitary plasmacytoma are based on combination of clinical, morphologic, immunologic, and radiologic features

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Most common primary malignant bone tumor
- Age
  - Patients usually > 30 years at time of diagnosis
    - Median age at diagnosis: ~ 70 years
- Sex
  - Males affected more frequently than females, M:F = 1.1:1.0

### Site

- May present as localized lesion (plasmacytoma) or as component of widespread disease (PCM)
- May involve any bone
- Most common sites are bones with active bone hematopoiesis
  - In order of frequency: Vertebrae, ribs, skull, pelvis, femur, clavicle, and scapula
  - Thoracic vertebrae are more commonly involved than cervical or lumbar
  - Long bone involvement below elbow or knee is rare

### Presentation

- Symptoms are generally attributable to end-organ damage
- Symptoms related to
  - Hypercalcemia
  - Renal insufficiency
  - Anemia
  - Bone lesions

### Natural History

- PCM
  - Usually incurable
- Solitary plasmacytoma
  - 2/3 of patients eventually evolve into generalized myeloma or additional solitary or multiple plasmacytomas
  - 1/3 of patients remain disease free for > 10 years

### Treatment

- Localized disease treated with resection or radiation
- PCM is incurable progressive disease
  - Range of survival varies from < 6 months to > 10 years (median: ~ 5.5 years)
  - Newer therapeutic approaches have significantly improved quality of life and survival
- Bone marrow transplantation is option for younger patients

## IMAGING

### Radiographic Findings

- 2/3 of cases show well-circumscribed, mixed, predominantly lytic pattern
- 1/3 show multicystic soap bubble or purely lytic appearance
- Geographic lytic lesion centered in bone marrow without identifiable matrix
- Lesions of long bones are also usually well circumscribed and may be encompassed by periosteal new bone formation, giving appearance of expansion
- Lesions in skull are well circumscribed and have punched-out appearance
- Rarely, PCM generates sclerotic lesions
  - May occur in setting of POEMS syndrome
  - May appear normal or "cold" on isotope scans

### MR Findings

- T1WI: Low signal intensity mass; enhancement with contrast
- Fluid-sensitive sequences
  - Intermediate signal intensity lesion
- MR imaging survey or PET scan is more sensitive than skeletal survey to rule out other lesion in plasmacytoma

## MACROSCOPIC

### General Features

- Friable, soft, and red or tan-white
- Underlying bone is eroded and fragile

## MICROSCOPIC

### Histologic Features

- Tumoral mass of plasma cells displacing normal bone marrow elements
- Myeloma plasma cells vary from mature forms indistinguishable from normal to immature, plasmablastic, and pleomorphic
  - Mature plasma cells
    - Eccentric nucleus with "spoke-wheel" or "clockface" chromatin without nucleoli
    - Basophilic cytoplasm and perinuclear hof
  - Plasmablasts
    - Immature forms have more dispersed nuclear chromatin, higher nuclear:cytoplasmic ratio, and, often, prominent nucleoli
  - Pleomorphic
    - Nuclear immaturity and pleomorphism rarely occur in reactive plasma cells and are reliable indicators of neoplastic plasma cells

## Diagnostic Criteria for Plasma Cell Myeloma

| Clonal Bone Marrow Plasma Cells 10% or Biopsy-Proven Plasmacytoma and Any 1 or More of the Following Myeloma Defining Events |
|---|
| Hypercalcemia |
| Serum calcium > 0.25 mmol/L higher than upper limit of normal |
| **Renal Insufficient** |
| **Creatinine clearance < 40 mL per minute or serum creatinine > 177 micromol/L** |
| Anemia |
| Hemoglobin value of > 20 g/L below lower limit of normal or hemoglobin value of < 100 g/L |
| Bone Lesions |
| 1 or more osteolytic lesions on skeletal radiography, CT, or PET/CT |
| **Any 1 or More of the Following Biomarkers of Malignancy** |
| Clonal bone marrow plasma cell percentage ≥ 60% |
| Involved:uninvolved serum free light chain ratio ≥ 100 |
| > 1 focal lesions on MR studies |

- Cytoplasmic immunoglobulin may produce variety of morphologically distinctive findings
  - Multiple pale bluish-white, grape-like accumulations (Mott cells, morula cells)
  - Cherry red refractive round bodies (Russell bodies)
  - Overstuffed fibrils (Gaucher-like cells)
  - Crystalline rods; pathognomonic of myeloma

## ANCILLARY TESTS

### Immunohistochemistry

- CD138 and CD38 are reliable markers of plasma cells
- IHC &/or ISH for light chains shows either kappa or lambda light chain-restricted plasma cell population
- CD19 is negative
- Neoplastic plasma cells may show aberrant expression of CD56, CD200, CD28, CD117, CD52, CD20, and CD10

### Flow Cytometry

- Monotypic cytoplasmic immunoglobulin
  - Usually lack surface immunoglobulin

### Genetic Testing

- PCM: Genetic abnormalities are detected by karyotype cytogenetics in 1/3 and by FISH in > 90% of cases
- Most frequent chromosome translocations involve heavy chain locus on chromosome 14q32
  - Common partners include: *CCND1* (11q13), *MAF* (16q23), *FGFR3/WHSC1* (MMSET) (4p16.3), *CCND3* (6p21), *MAFB* (20q11)
- FISH is often used to stratify risk of aggressive behavior
  - Presence of del(17p) &/or translocation t(4;14) &/or translocation t(14;16) is associated with aggressive clinical behavior

## DIFFERENTIAL DIAGNOSIS

### Metastatic Carcinoma and Lymphoma

- Poorly differentiated neoplastic cells may mimic other poorly differentiated tumors
  - Problematic on frozen section; however, diagnosis can usually be readily made on touch preparation

### Chronic Osteomyelitis With Plasma Cell Infiltration

- Plasma cells in osteomyelitis are polyclonal
- Fibrosis often prominent

### B-Cell Lymphoma

- PCM may show strong cyclin D1 expression, finding characteristic of mantle cell lymphoma

### POEMS Syndrome

- Osteosclerotic lesions associated with
  - Polyneuropathy, organomegaly, endocrine abnormalities, M protein, skin changes

### Reactive Plasmacytosis

- Plasma cells are polyclonal

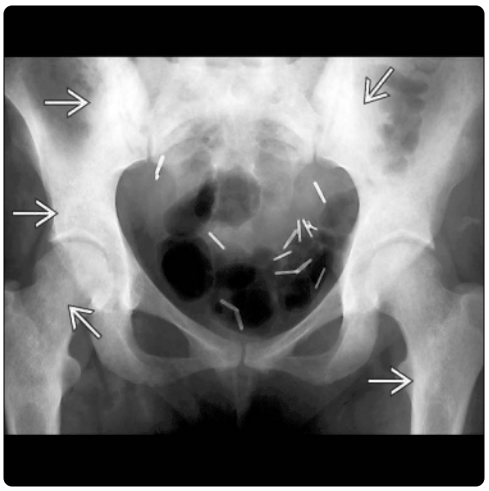
### Lymphoplasmacytic Lymphoma

- IgM monoclonal protein
- Contains many small lymphocytes

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### Sclerotic Myeloma



### Lytic Expansile Mass With Trabeculations



**(Left)** *Plain radiograph shows diffuse sclerosis in the innominate bones and proximal femora in this patient with sclerosing myeloma. Fewer than 3% of myeloma patients show bone sclerosis. This appearance could easily be confused with metastatic disease.* **(Right)** *Plain radiograph of multiple myeloma involving the ischial and pubic bones shows a large lytic lesion with a reticulated appearance. The diagnosis was confirmed on biopsy.*

### Large Lytic Tumor of Ilium

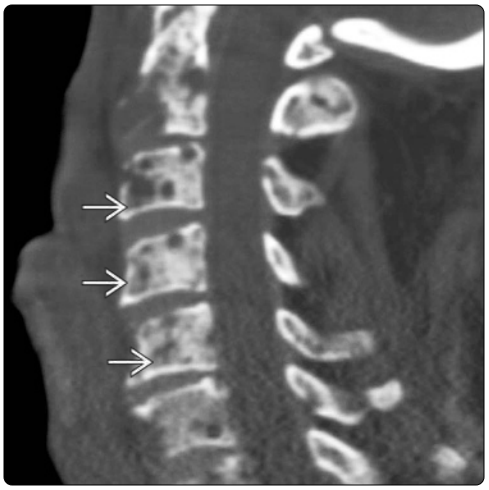


### Destructive Mass



**(Left)** *Axial CT shows plasma cell myeloma involving the ischium. The lytic lesion expands the bone and is associated with a mild periosteal reaction.* **(Right)** *Axial CT shows an expansile lytic and highly destructive lesion of the ilium. The cortex adjacent to the lesion is completely destroyed. Periosteal reaction is conspicuously absent in this example of plasmacytoma.*

### Lytic Lesions in Vertebral Column



### Oval Mass in Medullary Cavity

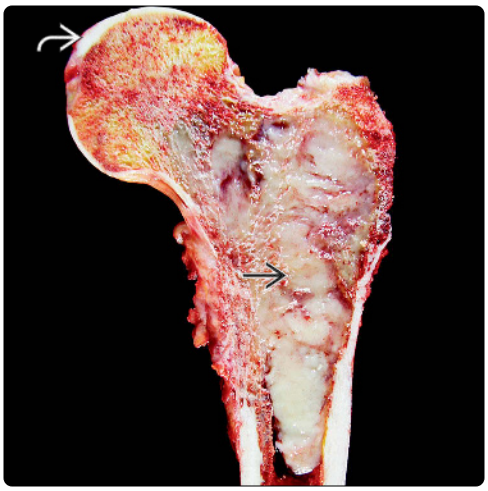


**(Left)** *CT of the lateral cervical spine from a skeletal survey demonstrates numerous lytic lesions in the bodies of the vertebrae. This patient met the diagnostic criteria for plasma cell myeloma.* **(Right)** *Coronal T1 MR shows a tumor with a signal intensity similar to the adjacent muscle. A biopsy confirmed a diagnosis of plasmacytoma.*

**Marrow Replacing Tumor**

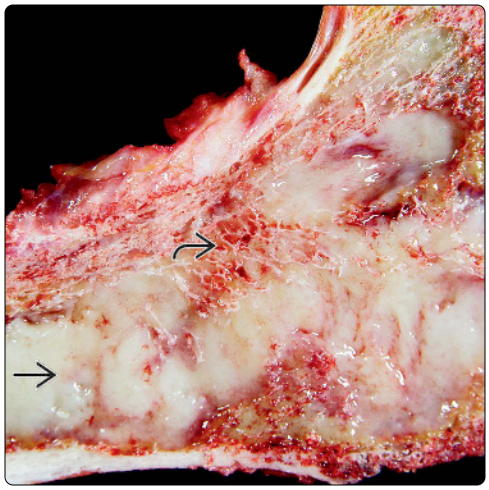


**Large, Tan-White Mass**



**(Left)** *T1 MR of the pelvis shows a tumor with a signal intensity similar to the adjacent muscle. The patient met the criteria for a plasma cell myeloma.* **(Right)** *Gross photograph of a resected femur involved by plasmacytoma shows a gray-white confluent lesion occupying the medullary space. The articular cartilage and subchondral bone appear free of tumor.*

**Nodules of Tumor Destroying Bone**

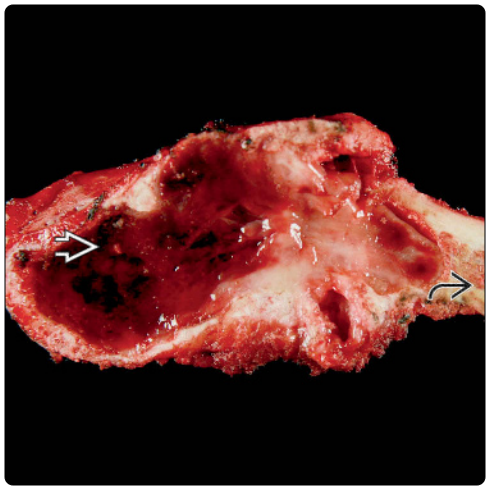


**Well-Circumscribed, Dark Red Mass**

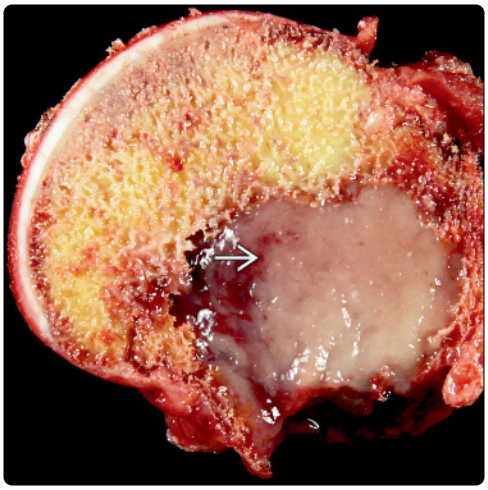


**(Left)** *Gross close-up photograph of plasmacytoma involving the neck of the femur shows the gray-white lesion diffusely infiltrating cancellous bone. Intervening foci of uninvolved bone are present.* **(Right)** *Gross photograph of a resected femoral head involved by plasmacytoma is shown. The lesion is well demarcated from surrounding cancellous bone. The tumor is soft and hemorrhagic. The adjacent cancellous bone is free of tumor.*

**Expansile Mass of Clavicle**

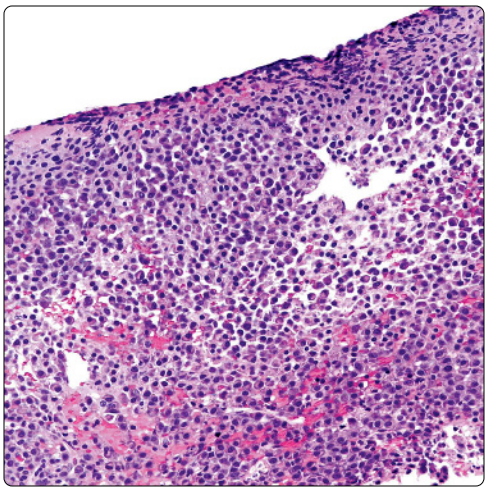


**Friable, Tan Mass**

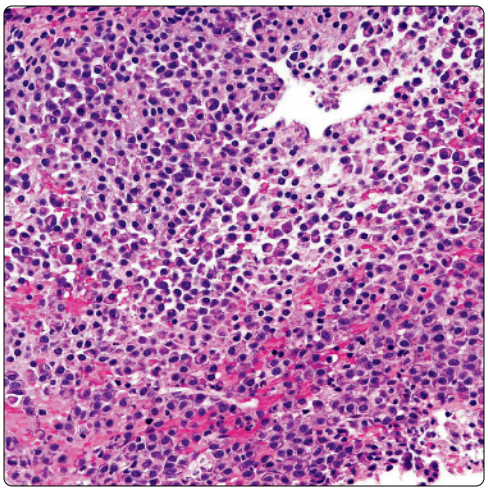


**(Left)** *Gross photograph of plasmacytoma involving the distal aspect of the clavicle shows bony expansion of the distal portion of the clavicle. A hemorrhagic and partially cystic intraosseous lesion is evident. The proximal portion of the clavicle is spared.* **(Right)** *Plasma cell myeloma involving the head of femur is shown. The articular cartilage and the subchondral bone was free of tumor. The lesion is tan white, fleshy, and well demarcated from the adjacent subchondral bone.*

### Sheets of Plasma Cells

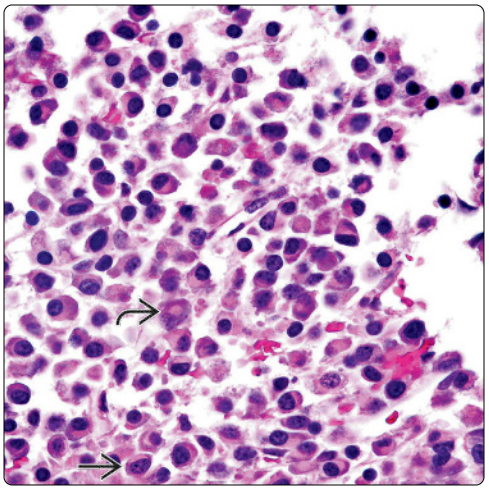


### Plasma Cells With Amphophilic Cytoplasm

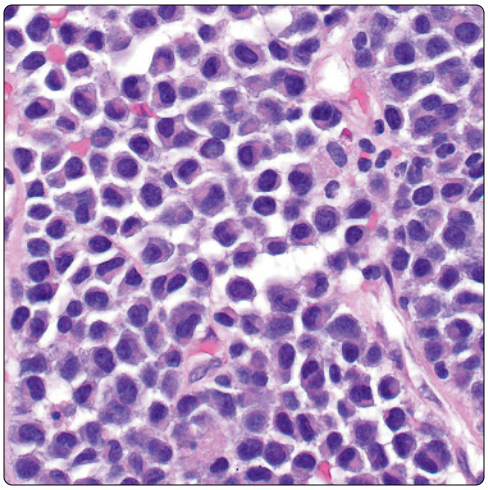


**(Left)** *Low-power H&E from a plasmacytoma is shown. The tumor is composed of a monotonous population of plasma cells. The dyshesive population of cells supports the diagnosis of a plasma cell neoplasm. A plasmacytoma may rarely form cohesive aggregates and thus resemble a carcinoma superficially.* **(Right)** *Photomicrograph of a plasmacytoma shows that the neoplastic plasma cells in this case have abundant amphophilic cytoplasm. The monotony of the cells and eccentric nuclei suggest the diagnosis of a plasmacytoma.*

### Plasma Cells With Perinuclear Hof

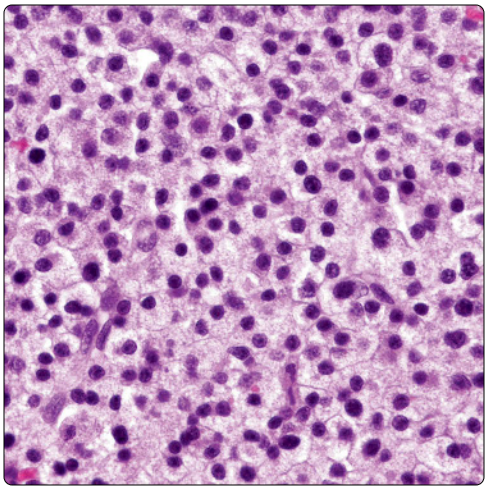


### Tumor Cells With Eccentric Nuclei

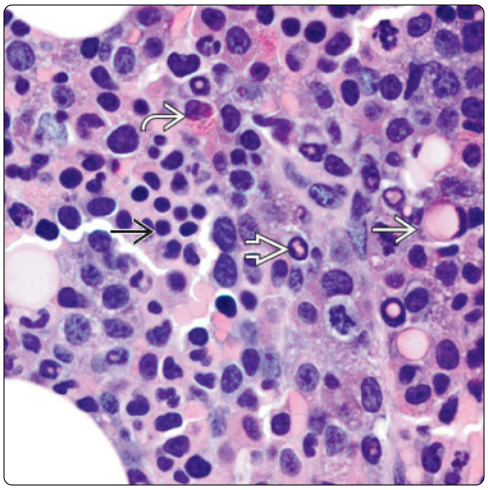


**(Left)** *High-power H&E of a plasmacytoma shows that the plasma cells appear mature with eccentric nuclei. The cells show the characteristic perinuclear hof ⇨ and clockface chromatin pattern ⇨.* **(Right)** *High-power H&E from a plasmacytoma shows the plasma cells appearing mature with eccentric nuclei. The perinuclear hof is only focally present. The clockface chromatin pattern, although seen, is not prominent.*

### Plasmacytoma With Clear Cytoplasm

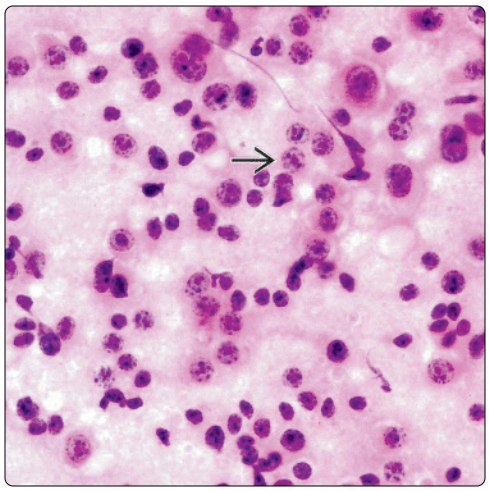


### Dutcher Bodies

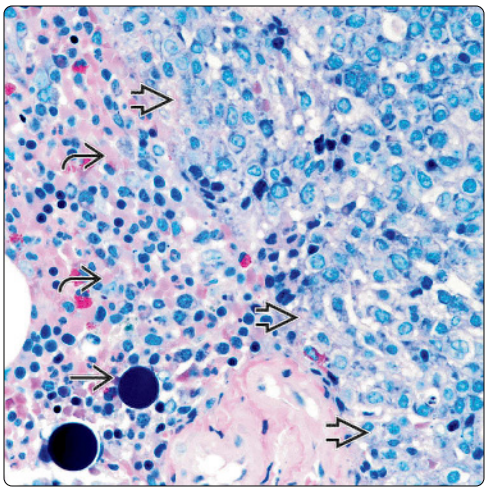


**(Left)** *Photograph of a plasmacytoma shows neoplastic plasma cells with abundant pale cytoplasm. The eccentric nuclei suggest the diagnosis of a plasmacytoma. The differential diagnosis includes epithelial and neuroendocrine tumors with clear cytoplasm.* **(Right)** *Bone marrow biopsy from a patient with myeloma shows erythroid ⇨ and myeloid elements ⇨. There is an increased number of plasma cells, some of which show intranuclear inclusions (Dutcher bodies) ⇨ as well as cytoplasmic Russell bodies ⇨.*

### Direct Smear

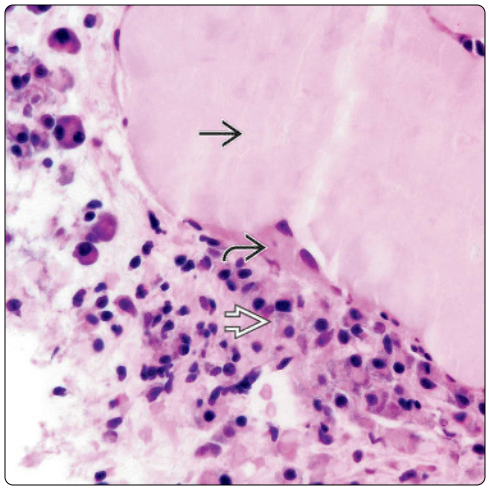


### Giemsa Stain

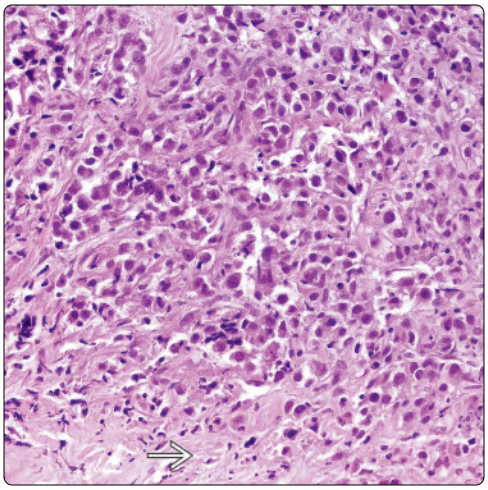


**(Left)** *Direct smear from a plasmacytoma predominantly shows plasma cells. The nuclear characteristics of plasma cells are well represented on this preparation, especially the clockface chromatin, making this a valuable tool in evaluating frozen sections.* **(Right)** *A Giemsa stain shows a nodular aggregate of plasma cells, a finding that supports the diagnosis of plasma cell myeloma. Nonneoplastic marrow is also present. Russell bodies are present within the nonneoplastic marrow.*

### Amyloid Deposition

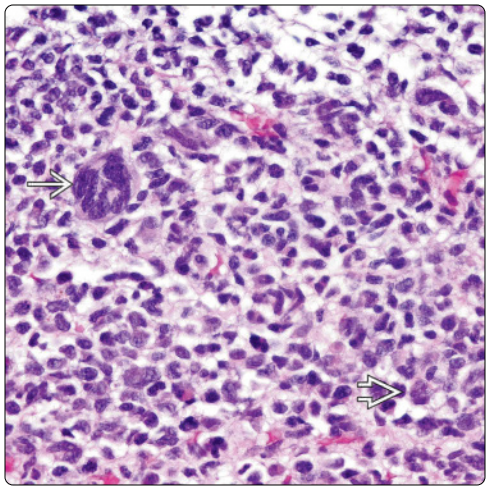


### Plasmacytoma Mimicking Carcinoma

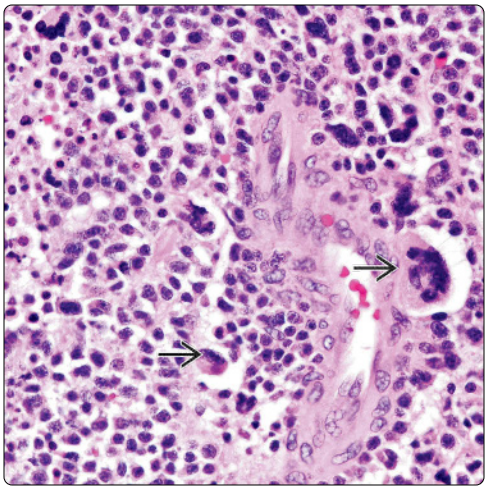


**(Left)** *Plasmacytoma with amyloid deposition is shown. A multinucleate giant cell is seen adjacent to the amyloid. The amyloid is composed of immunoglobulin light chains. This material showed apple green birefringence on a Congo red stain. Plasma cells are also present.* **(Right)** *Plasmacytoma associated with a desmoplastic stromal reaction is shown. The packeted appearance of the neoplastic cells mimics a metastatic carcinoma. The eccentrically placed nuclei would favor a plasmacytoma.*

### Plasmacytoma With Anaplastic Features

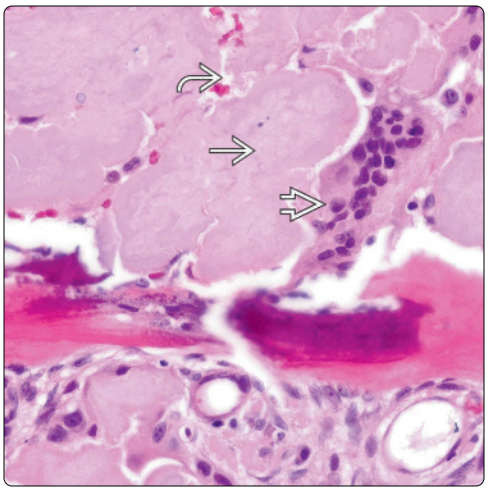


### Bizarre Tumor Cells

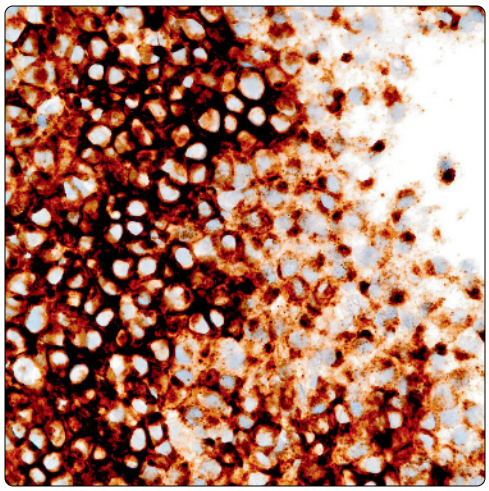


**(Left)** *Plasmacytoma with anaplastic features is shown. Bizarre tumor giant cells are present. The cells show marked nuclear atypia and many cells lack the cytologic features of plasma cells. The tumors cells were positive for CD138 and kappa and negative for lambda light chain.* **(Right)** *Plasmacytoma with anaplastic features shows occasional markedly pleomorphic and multinucleate plasma cells. The majority of neoplastic plasma cells are mononuclear and lack this bizarre nuclear atypia.*

### Abundant Amyloid Deposition

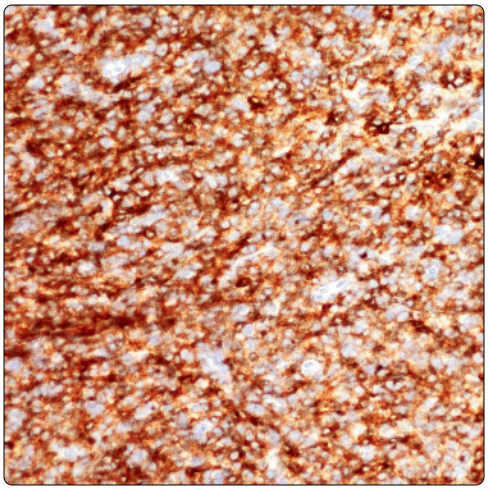


### CD138 Stain

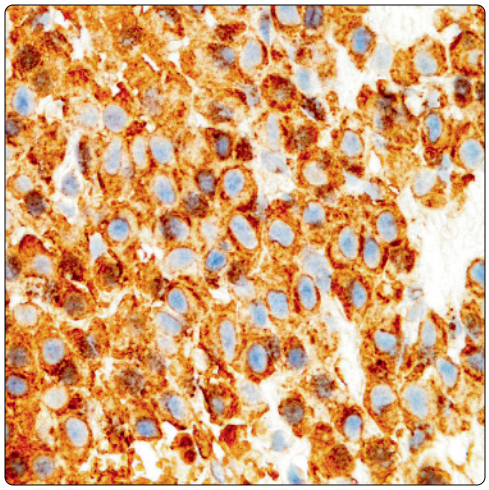


**(Left)** *Plasmacytoma with abundant amyloid deposition is shown. The amyloid is seen as dense eosinophilic material and is associated with a cracking artifact. Giant cell reaction to the amyloid is also seen. The neoplastic plasma cells are not seen in this image.* **(Right)** *This plasmacytoma is diffusely positive for CD138 immunohistochemically. Benign and neoplastic plasma cells show membranous and cytoplasmic reactivity for CD138. Metastatic carcinomas are also positive for CD138.*

### Plasmacytoma Reactive for EMA

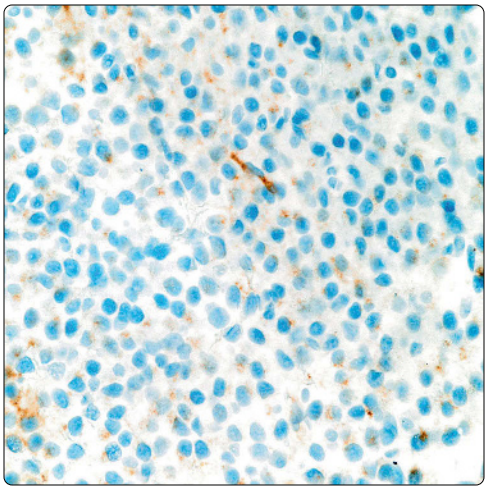


### Positive for Lambda Light Chain

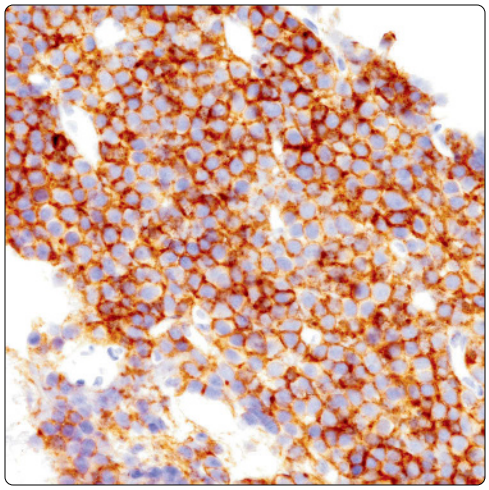


**(Left)** *Plasmacytoma with diffuse reactivity for EMA is shown. Plasmacytomas may occasionally stain for EMA, and thus mimic an epithelial neoplasm. Plasma cell neoplasms are negative for keratin.* **(Right)** *This in situ hybridization stain for lambda light chain demonstrates that all of the neoplastic cells show diffuse cytoplasmic reactivity for lambda light chain.*

### In Situ Hybridization Stain



### Plasmacytoma Reactive for CD117



**(Left)** *This in situ hybridization stain for kappa light chain shows the plasma cells are negative. In conjunction with the diffuse reactivity for lambda light chain, this finding confirms the monoclonality of this tumor. In comparison to immunohistochemistry, the in situ platform is typically associated with a less nonspecific signal.* **(Right)** *Plasmacytoma shows diffuse reactivity for C-kit (CD117). Normal plasma cells are typically negative for CD117. Lack of expression of CD117 has been associated with aggressive disease.*

# Mast Cell Disease

KEY FACTS

## TERMINOLOGY

- Mastocytosis is due to clonal, neoplastic proliferation of mast cells
- Systemic mastocytosis: Characterized by involvement of ≥ 1 extracutaneous organ ± skin lesions

## CLINICAL ISSUES

- Propensity to involve bones of trunk and proximal extremities
- Usually has long, relatively benign, clinical course
- May occur at any age, including childhood
- May be multifocal in bones
- Symptoms related to histamine (substance produced in abundance by mast cells)
- Treatment of indolent disease is based on symptom control
- Chemotherapy has not been shown to be effective in any form of disease
- May occur at any age, including childhood
- Usually has long, relatively benign clinical course

## IMAGING

- Multifocal sclerotic lesions or mixed sclerotic and lytic lesions
- Can present as diffuse osteosclerosis or osteoporosis
- Diffuse osteoporosis associated with pathological fractures, especially vertebra

## MACROSCOPIC

- Effected marrow is tan-white, and trabecular bone is sclerotic

## MICROSCOPIC

- Mast cells may appear morphologically normal or spindle-shaped

## ANCILLARY TESTS

- Mast cells stain for CD117 (C-kit) and CD25
- Activating mutation of *KIT* (c-KIT) gene is identified in > 95% of cases, most commonly involving codon 816

**Multiple Sclerotic Lesions**

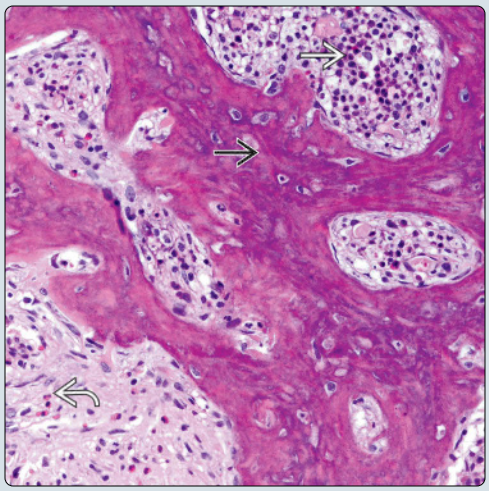


**Dense Lesions**

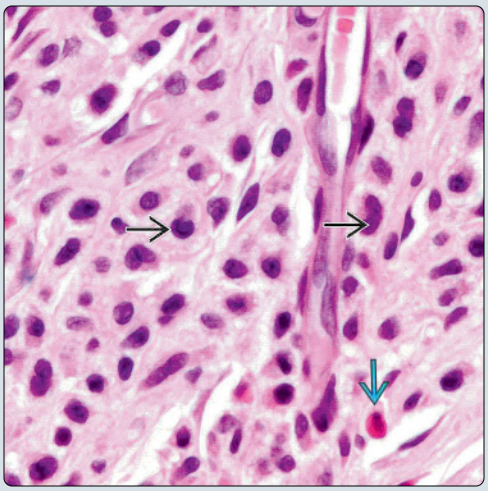


**(Left)** *Plain radiograph of the pelvis in a patient with mastocytosis shows a single sclerotic lesion in the ischium. Such a lesion in an elderly man is far more likely to represent a metastasis.* **(Right)** *Axial CT from a patient with mastocytosis shows a single well-circumscribed sclerotic lesion in the ilium. Multiple other sclerotic lesions are present elsewhere in the pelvis of this individual.*

**Sclerotic Lesion**



**Numerous Mast Cells**



**(Left)** *The medullary cavity is replaced by numerous mast cells that are associated with reactive fibrosis and scattered eosinophils. The bone sclerosis manifests as interconnecting trabeculae of reactive woven bone.* **(Right)** *Mastocytosis manifests as numerous mast cells that are intermediate in size, round to oval nuclei that have fine chromatin or are dark staining, and eosinophilic cytoplasm. The mast cells are enmeshed in reactive fibrous tissue, and eosinophils are present.*

## TERMINOLOGY

### Synonyms

- Mastocytosis

### Definitions

- Mastocytosis is clonal, neoplastic proliferation of mast cells
  - Cutaneous mastocytosis: Disease is confined to skin
  - Systemic mastocytosis: Characterized by involvement of ≥ 1 extracutaneous organ ± skin lesions
    - Bone marrow frequently affected
  - Mast cell leukemia and mast cell sarcoma are rare

## CLINICAL ISSUES

### Epidemiology

- Age
  - May occur at any age, including childhood
- Sex
  - No predilection

### Site

- Propensity to involve bones of trunk and proximal extremities
  - May be multifocal in bones
- Extraosseous disease
  - Cutaneous involvement in 80% of cases
  - Other commonly involved organs include spleen, lymph nodes, liver, and gastrointestinal tract mucosa

### Presentation

- Urticaria pigmentosa seen in patients who have cutaneous involvement
- Constitutional symptoms, such as fatigue
- Mediator-related systemic events
  - Important mediators are histamine and heparin
    - Cause edema, flushing, hypotension, tachycardia, anaphylaxis, and dyspnea
  - Heparin may underlie focal lytic lesions and diffuse osteoporosis

### Treatment

- Treatment of indolent disease is based on symptom control
- Chemotherapy not effective in any form of disease

### Prognosis

- Usually has long, relatively benign clinical course
- Patients with leukemic form may survive for only 1-2 years
- Minority of patients may die of secondary complications: Severe gastrointestinal hemorrhage
- Adulthood onset may have more aggressive course

## IMAGING

### Radiographic Findings

- Multifocal sclerotic lesions or mixed sclerotic and lytic lesions
  - Multifocal sclerotic lesions may progress
- Can present as diffuse osteosclerosis or osteoporosis
  - Diffuse osteoporosis associated with pathological fractures, especially vertebra

### MR Findings

- Abnormalities parallel pathological marrow involvement
- Involved areas have increase signal intensity on T2 and stir pulse signals

### CT Findings

- Sclerotic lesions manifest as areas of increased density
- CT may demonstrate hepatosplenomegaly and lymphadenopathy

### Bone Scan

- Normal, unifocal, multifocal, or show diffuse skeletal avidity

## MACROSCOPIC

### General Features

- Lesions vary in size
- Effected marrow is tan-white, and trabecular bone is sclerotic

## MICROSCOPIC

### Histologic Features

- Multifocal compact aggregates of mast cells
- Round hyperchromatic nuclei with moderate amount of pale cytoplasm and tiny basophilic cytoplasmic granules
- Mast cells often normal in appearance; may be spindled or contain few cytoplasmic granules
- Mast cells have paratrabecular arrangement with fibrosis and eosinophils
- Involved trabecular bone is sclerotic

## ANCILLARY TESTS

### Histochemistry

- Giemsa stain
  - Mast cells contain numerous small uniform cytoplasmic granules highlighted by stain

### Immunohistochemistry

- Benign and neoplastic mast cells stain for CD117 (C-kit) and tryptase
- Neoplastic mast cells are positive for CD25; benign and reactive mast cells are negative

### Genetic Testing

- Activating mutation of *KIT* (c-KIT) gene is identified in > 95% of cases, most commonly involving codon 816
  - Detecting mutation can be diagnostically useful
  - Mutation is resistant to tyrosine kinase inhibitor imatinib

## DIFFERENTIAL DIAGNOSIS

### Reactive Mast Cell Proliferations

- Benign and reactive mast cells are negative for CD25

## SELECTED REFERENCES


1. Ustun C et al: Advanced systemic mastocytosis: from molecular and genetic progress to clinical practice. Haematologica. 101(10):1133-1143, 2016
2. Pardanani A: Systemic mastocytosis: disease overview, pathogenesis, and treatment. Hematol Oncol Clin North Am. 26(5):1117-28, 2012
3. Brunning RD et al: Systemic mastocytosis. Extracutaneous manifestations. Am J Surg Pathol. 7(5):425-38, 1983

# Erdheim-Chester Disease

KEY FACTS

## TERMINOLOGY

- Histiocytic proliferation, which is caused by marrow infiltration of lipid-laden histiocytes causing diffuse and symmetric fibrosis and bone sclerosis

## ETIOLOGY/PATHOGENESIS

- Many lesions have *BRAF* V600E mutation

## CLINICAL ISSUES

- Usually arises in older individuals with peak incidence between 5th-7th decades of life
- Most frequently affects long tubular bones
- Can also arise in other bones, such as ribs, vertebrae, and craniofacial skeleton
- Pain and swelling
- Some patients die due to extraosseous involvement

## IMAGING

- Bilateral, symmetric, diffuse sclerosis of diaphysis and metaphysis with sparing of epiphyses
- Bone scan shows increased symmetric uptake of affected regions

## MACROSCOPIC

- Firm and yellow

## MICROSCOPIC

- Diffuse infiltration of lipid-laden (foamy) histocytes
- Fibrosis, sclerosis of bone

## ANCILLARY TESTS

- Immunohistochemically, neoplastic cells express CD68, CD163, and BRAF

## DIAGNOSTIC CHECKLIST

- Think ECD in patient with diffuse symmetrical sclerosis of long bones and marrow replaced by infiltrate of foamy macrophages with scattered mononuclear cells and fibrosis

**Sclerosis of Femur and Tibia**



*Radiograph of Erdheim-Chester disease shows diffuse sclerosis of the medullary bone involving the metaphysis and diaphysis of the femur and proximal tibia. There appears to be minimal involvement of the epiphysis.*

**Tan-Yellow Tissue Replaces Bone**



*Erdheim-Chester disease involving the distal aspect of the femur shows that the marrow space is filled by a bright yellow and gray lesion.*

## TERMINOLOGY

### Abbreviations

- Erdheim-Chester disease (ECD)

### Synonyms

- Lipogranulomatosis
- Lipid granulomatosis
- Polyostotic sclerosing histiocytosis

### Definitions

- Histiocytic proliferative disorder caused by infiltration of lipid-laden histiocytes producing diffuse and symmetric bony fibrosis and sclerosis with frequent extraskeletal involvement

## ETIOLOGY/PATHOGENESIS

### Genetics

- Many lesions have *BRAF* V600E mutation
  - Mutation detectable in monocytes in blood: Clonal disease
  - Amino acid substitution of glutamic acid for valine at position 600 of BRAF protein
    - Found in > 50% of patients
  - Associated with activation of local and systemic proinflammatory cytokine-chemokine network
    - Elevated levels of interferon, interleukin 6 and 12, and monocyte chemotactic protein 1
- Activation of MAPK pathway
- Some patients may be wild type for *BRAF* but have mutation in *NRAS* or *PIK3CA*

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Extremely rare
- Age
  - Usually arises in older individuals with peak incidence between 5th-7th decades of life
    - Most patients are > 40 years at time of diagnosis
- Sex
  - Males are affected slightly more frequently than females

### Site

- Skeleton involved in virtually all patients
- Long tubular bones are typically involved
  - Distal ends of femur and proximal and distal ends of tibia are most common sites
  - Distribution is often bilateral and symmetrical
  - Infrequently affects other bones, such as ribs, vertebrae, and craniofacial skeleton

### Presentation

- Clinical spectrum is broad
  - Depends on distribution and extent of lesions
- Bone pain and swelling
- Fever and weight loss
- Various extraosseous manifestations are related to organ systems affected by proliferative histiocytic process
  - Cardiac and pulmonary symptoms
  - Orbital and retroperitoneal masses
  - Xanthelasma-like lesions of skin
  - Diabetes insipidus when involving craniofacial skeleton
  - Neurological symptoms

### Treatment

- Interferon alpha
- Anticytokine therapy
- Serine/threonine kinase inhibitors of *BRAF* with V600E mutation
- MAPK pathway inhibition

### Prognosis

- Overall prognosis is poor
  - Patients may die due to severe multiorgan system involvement by inflammatory infiltrate

## IMAGING

### Radiographic Findings

- Bilateral, symmetrical, cortical, and intramedullary sclerosis of diaphysis and metaphysis
  - Sparing of epiphyses
- Obliteration of margin between cortex and medullary space
- Periosteal new bone may be present

### MR Findings

- Low T1 signal intensity and high T2 signal intensity with diffuse marrow abnormality
- Marrow infarction may be seen

### CT Findings

- Central medullary osteosclerosis
- Associated visceral and retroperitoneal involvement may be seen

### Bone Scan

- Shows increased symmetric uptake of affected regions

## MACROSCOPIC

### General Features

- Firm and yellow
- Bony trabeculae may be thickened

## MICROSCOPIC

### Histologic Features

- Diffuse infiltration of lipid-laden (foamy) histocytes
  - Scattered lymphocytes and plasma cells are common
- Marrow fibrosis
- Rebuttressing (sclerosis) of preexisting bone
  - Reactive woven bone often present
- Scattered Langerhans cells may be present
- Touton-type giant cells can be seen
- Cholesterol clefts may be numerous

## ANCILLARY TESTS

### Immunohistochemistry

- Foamy histiocytes express histiocytic markers CD68 and CD163
  - Foamy macrophages may be BRAF(+)

- Scattered Langerhans cells within lesion express S100 protein, langerin, and CD1a
  - Foamy macrophages are negative for these markers

### Genetic Testing

- Foamy histiocytes and circulating monocytes have *BRAF* V600E mutation

### Electron Microscopy

- Histiocytic cells have lysozymes and abundant intracytoplasmic lipid droplets
- Birbeck granules are absent in foamy histiocytes but present in Langerhans cells

## DIFFERENTIAL DIAGNOSIS

### Langerhans Cell Histiocytosis (Eosinophilic Granuloma)

- Histiocytes in eosinophilic granuloma do not contain intracytoplasmic lipid and are not foamy in appearance
- Langerhans cells have hyperlobated and cleaved nuclei unlike those of ECD
- Langerhans cells stain strongly for S100 protein, CD1a, and langerin
- Langerhans cell histiocytosis is associated with *BRAF* V600E mutation

### Rosai-Dorfman Disease

- Bone involvement in Rosai-Dorfman disease shows diffuse infiltration by histiocytes that have eosinophilic cytoplasm
  - Emperipolesis is characteristic finding in Rosai-Dorfman disease
  - Histiocytes in Rosai-Dorfman disease are S100 protein (+) unlike histocytes in ECD, which are S100(-)
  - Distribution of lesions is usually not bilateral and symmetrical
- Rosai-Dorfman disease does not have *BRAF* mutation

### Gaucher Disease

- Gaucher cells have eosinophilic cytoplasm that has wrinkled tissue paper appearance
- Gaucher disease is often associated with osteonecrosis
- Bone in Gaucher disease is not sclerotic
- Diffuse osteoporosis and radiologic Erlenmeyer flask deformity present in Gaucher disease
- Sclerosis in Gaucher disease results from marrow infarctions
- Does not have mutation in *BRAF*

### Xanthoma of Bone

- Radiographically presents as single lytic lesion of bone and does not produce diffuse symmetrical osteosclerosis
- Patient may have systemic lipid abnormality

### IgG4-Related Disease

- Storiform fibrosis is present and absent in ECD
- Venous obliteration is typical and absent in ECD
- Increase in IgG:IgG4 ratio in IgG4 disease is absent in ECD
- Foamy macrophages are not prominent
- Lacks mutation in *BRAF* V600

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Think ECD in patient with diffuse symmetrical sclerosis of long bones and marrow replaced by infiltrate of foamy macrophages with scattered lymphocytes and plasma cells and fibrosis

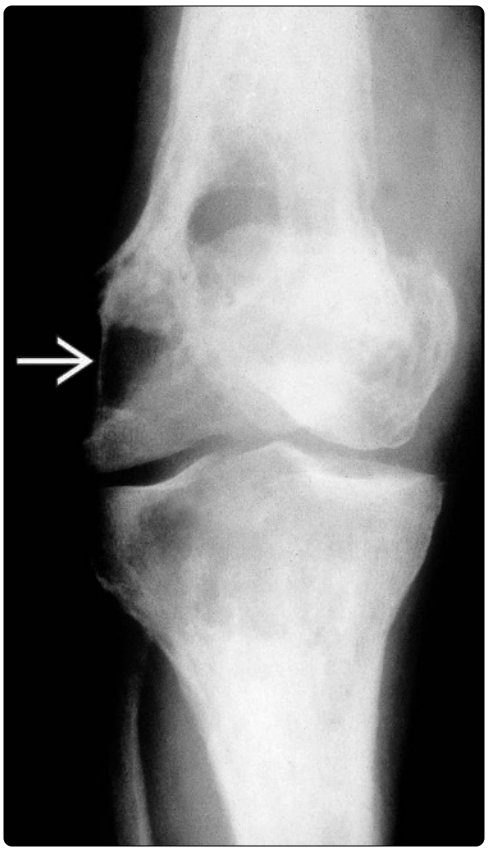
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Sclerosis of Diaphysis

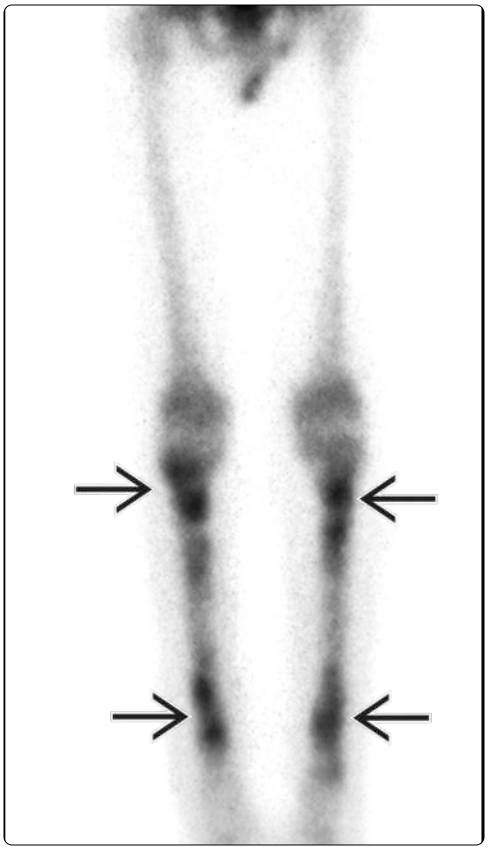


Mixed Sclerotic and Lytic Changes

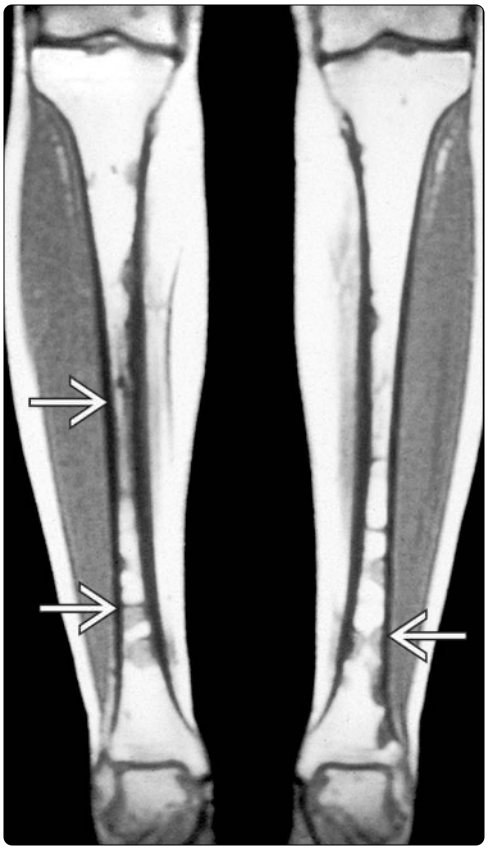


**(Left)** *A plain x-ray of Erdheim-Chester disease involving the tibia demonstrates patchy sclerosis of the medullary bone in the metaphysis and diaphysis. This is consistent with Erdheim-Chester disease but is much less extensive than is typically seen.* **(Right)** *Radiograph of the knee shows dense sclerosis of the marrow of the distal femur and proximal tibia. The epiphyses are relatively spared. There is also focal destruction of the medial cortex of the distal femur. This type of aggressive bone destruction can be seen in Erdheim-Chester disease.*

Avid Uptake on Bone Scan



Symmetric Involvement



**(Left)** *This radioisotope bone scan demonstrates diffuse bilateral increased uptake in the lower limbs, especially below the knees. The increased uptake predominantly affects the metaphysis and diaphysis.* **(Right)** *Coronal T1WI MR of Erdheim-Chester disease of the tibia demonstrates patchy marrow replacement in the diaphysis and metaphysis on a background of normal marrow signal. The epiphysis does not appear to be involved.*

**Sclerosis of Femur**



**Yellow Deposits of Foamy Macrophages**

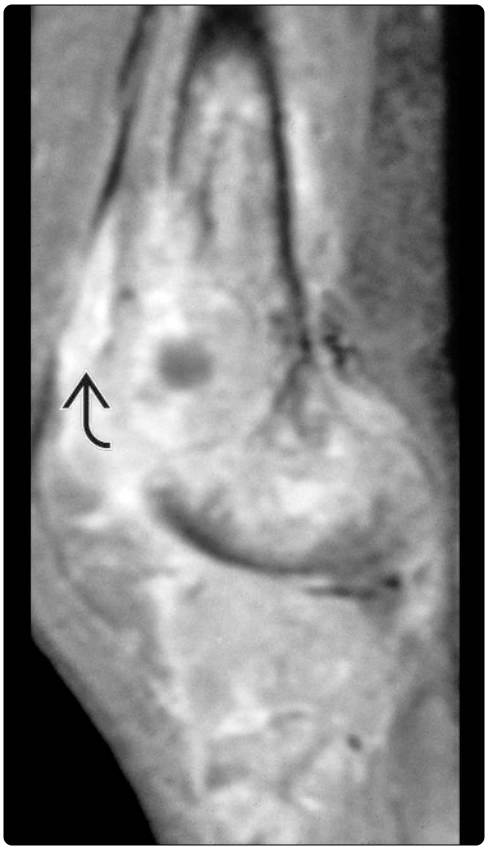


**(Left)** *Lateral radiograph of the femur shows changes that are characteristic of Erdheim-Chester disease. The bone demonstrates prominent areas of sclerosis ➡ with scattered lucencies ⇨. There is no periosteal reaction.* **(Right)** *The distal aspect of the femur shows yellow-white infiltrative tissue that replaces the medullary cavity and overlying anterior cortex. The lesion involves the metaphysis and extends into the proximal epiphysis. Notice that portions of the lesions are sharply demarcated ➡.*

**Sclerotic and Lytic Lesions**

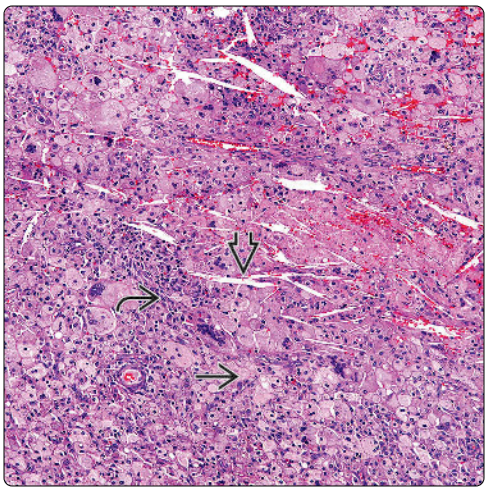


**Extensive Bone Disease**

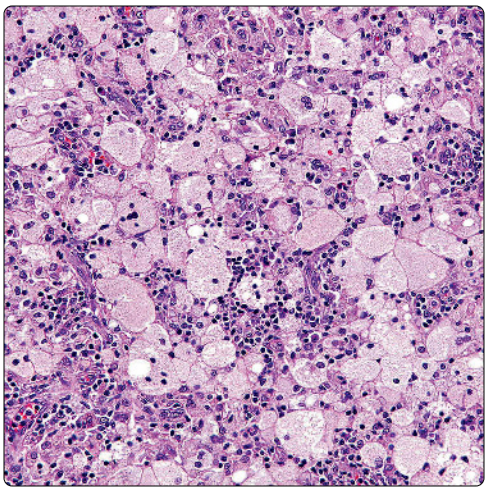


**(Left)** *Lateral radiograph of the knee in patient with Erdheim-Chester disease shows large irregular regions of sclerosis ⇨ and bone destruction ➡. Despite the extensive changes, there is no appreciable periosteal reaction.* **(Right)** *Sagittal T2WI MR of the femur in Erdheim-Chester disease shows extensive marrow signal abnormality, with heterogenous signal abnormality involving the distal femur and the proximal tibia. The abnormal tissue destroys the anterior cortex and involves the adjacent soft tissues ⇨.*

Numerous Foamy Macrophages

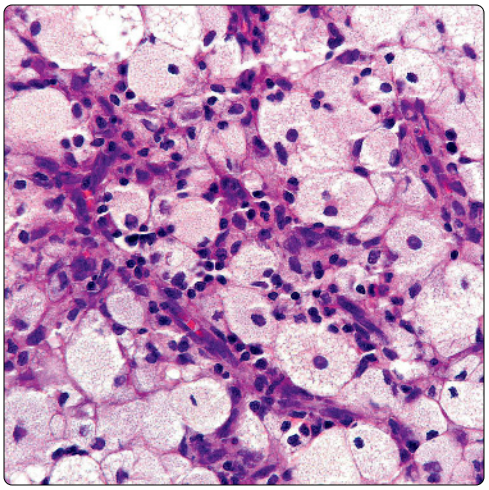


Large Histiocytes

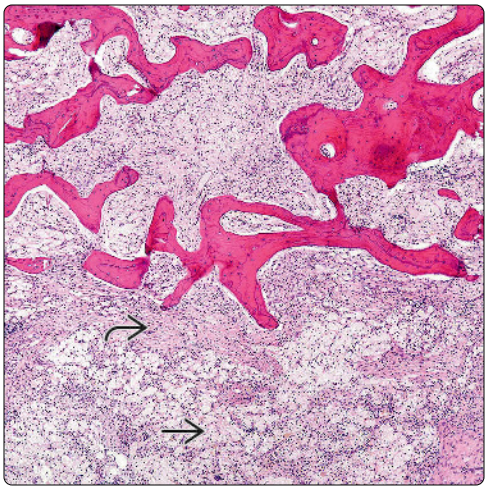


**(Left)** *This Erdheim-Chester disease of bone consists of large collections of foamy histiocytes with finely vacuolated granular eosinophilic cytoplasm admixed with chronic inflammatory cells. There is focal hemorrhage with cholesterol clefts.* **(Right)** *High-power view of Erdheim-Chester disease shows a collection of foamy histiocytes and chronic inflammatory cells. The histiocytes have abundant finely vacuolated cytoplasm and small centrally located nuclei.*

Foamy Macrophages

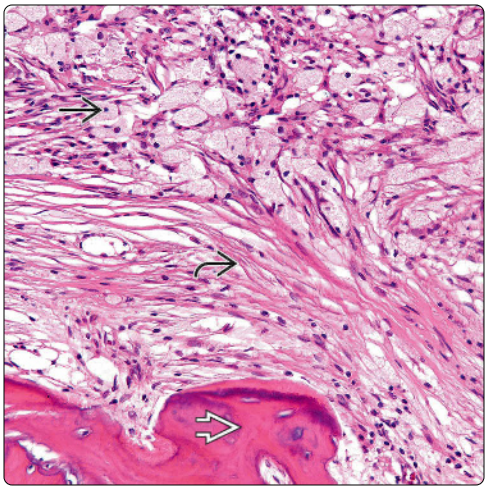


Inflammation With Sclerotic Bone

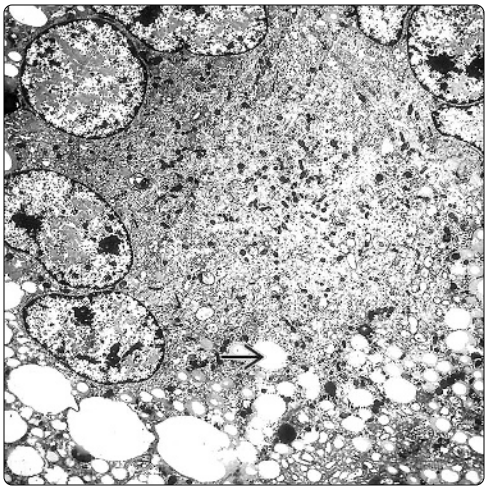


**(Left)** *A very high-power view of Erdheim-Chester disease of bone shows that the foamy histiocytes have finely granular eosinophilic cytoplasm and small nuclei. Surrounding the histiocytes are chronic inflammatory cells that are mostly lymphocytes.* **(Right)** *In this Erdheim-Chester disease of bone, the marrow spaces have been replaced by sheets of foamy histiocytes with intervening areas of fibrosis. The bone is abnormally thickened with prominent cement lines.*

Foamy Macrophages and Fibrosis



Ultrastructure of Foamy Macrophage



**(Left)** *Erdheim-Chester disease of bone shows a collection of foamy histiocytes that have centrally located nuclei, as well as scattered chronic inflammatory cells. The stroma is fibrotic, and the bone is thickened.* **(Right)** *An electron micrograph of Erdheim-Chester disease shows histiocytic cells with abundant cytoplasm that contains lipid droplets and scattered mitochondria. The nuclei are round and regular in size and shape.*

# Rosai-Dorfman Disease

KEY FACTS

## TERMINOLOGY

- Disease of unknown etiology characterized by proliferation of large histiocytes

## CLINICAL ISSUES

- Broad age distribution (1.5-63 years) for intraosseous lesions; most are adults
- Patients with bone involvement usually have extraskeletal disease, especially in lymph nodes
- When involving skeleton, Rosai-Dorfman disease (RD) can develop in variety of bones
- Patients present with localized pain or swelling
- When involving spine and sacrum, lesion can extend into spinal canal and cause neurologic symptoms
- Some lesions may be asymptomatic and discovered incidentally
- Prognosis is very good

## IMAGING

- Lytic, typically centered in medullary cavity; usually well circumscribed; may be ill defined

## MICROSCOPIC

- Lesional cells replace marrow spaces encasing preexisting trabecular bone and infiltrate through haversian systems
- Composed of numerous large histiocytes that have vesicular nuclei with conspicuous nucleoli and abundant eosinophilic cytoplasm
- RD histiocytes engulf leukocytes within their cytoplasm; known as emperipolesis

## ANCILLARY TESTS

- Histiocytes stain S100 protein, CD68, and CD163 (+); CD1a, langerin, and BRAF (-)

## TOP DIFFERENTIAL DIAGNOSES

- Osteomyelitis, Langerhans cell histiocytosis, Erdheim-Chester disease

**Lytic Lesion in Skull**

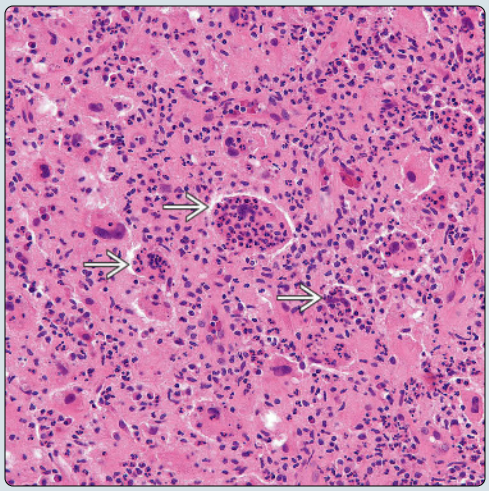


**Soft Tan-Brown Mass**

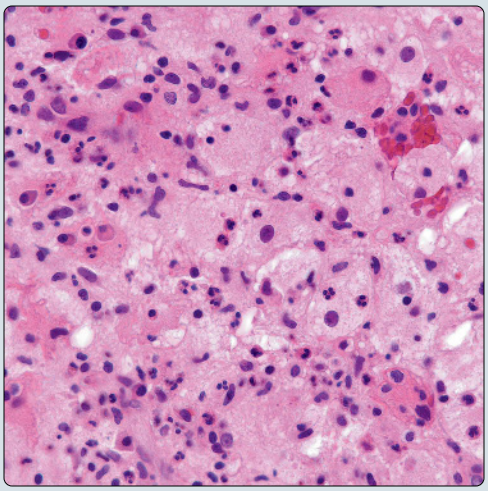


**(Left)** *A lateral skull radiograph of Rosai-Dorfman disease (RD) of bone shows a lytic lesion involving the occiput. The lesion is centered over the middle table and therefore probably arose in medullary bone.* **(Right)** *In this RD of the skull, the tumor has replaced the cortical bone. The tumor has a tan-brown appearance and is well demarcated from the surrounding bone on each side.*

**Numerous Large Histiocytes**



**Emperipolesis**



**(Left)** *In this primary intraosseous RD of bone, the large histiocytes demonstrate prominent emperipolesis of lymphocytes, neutrophils, and plasma cells* ➡. **(Right)** *Sheets of Rosai-Dorfman cells are present and contain round to oval nuclei with fine chromatin and small nucleoli. The cells have abundant cytoplasm with evidence of phagocytosis of inflammatory cells.*

## TERMINOLOGY

### Abbreviations

- Rosai-Dorfman disease (RD)

### Synonyms

- Sinus histiocytosis with massive lymphadenopathy

### Definitions

- Disease of unknown etiology characterized by proliferation of distinctive histiocytes

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Very rare disease; exact incidence is unknown
- Age
  - Intraosseous tumors can affect all age groups; mean age: 28 years
- Sex
  - More common in female patients

### Site

- Most cases arise in lymph nodes; rarely develops in extranodal sites
- Most frequent extranodal sites are skin, upper respiratory tract, and bone
- Patients with bone involvement usually also have extraskeletal disease
  - Can also affect skeleton without any identifiable extraskeletal involvement
- When involving skeleton, RD can develop in variety of bones
  - Has been reported to involve radius, femur, skull, tibia, fibula, maxilla, spine, pelvis, sacrum, metacarpal, phalanx, talus, clavicle, triquetrum

### Presentation

- Localized pain, swelling, tenderness
- When involving spine and sacrum, tumor can extend into spinal canal and cause neurologic symptoms
- Some lesions may be asymptomatic and discovered incidentally

### Natural History

- Depends upon extent of nodal and extranodal disease
- In most cases, clinical course is relatively benign and indolent

### Treatment

- Lesions of skeleton have been adequately treated with curettage

### Prognosis

- Usually very good; RD may be associated with development of new bone lesions or with lymph node involvement

## IMAGING

### Radiographic Findings

- Lytic, usually centered in medullary cavity; does not have predilection for any region of bone
- Often well circumscribed with sclerotic margins
- There may be destruction of cortex associated with periosteal reaction; pathologic fractures are rare
- May be solitary or multifocal and affect both axial and appendicular skeleton
- Resembles osteomyelitis on imaging but is more mass-like and less edematous
- Can resemble eosinophilic granuloma in that it is usually purely lytic but sometimes associated with rim of reactive sclerosis

## MICROSCOPIC

### Histologic Features

- Lesions exhibit classic morphological features
  - Disease process replaces marrow spaces encasing preexisting trabecular bone and percolates through haversian systems
  - Composed of numerous large histiocytes that have abundant eosinophilic cytoplasm containing engulfed leukocytes
    - Large histiocytes frequently contain intracytoplasmic lymphocytes, plasma cells, or neutrophils (so-called emperipolesis)
- Nuclei of histiocytes are vesicular with finely stippled chromatin, occasionally prominent nucleoli, and smooth contours; no folds or clefts
- Cellular mixed inflammatory infiltrate containing lymphocytes, neutrophils, and eosinophils
- Focal necrosis and collection of epithelioid histiocytes mimicking granulomas may be seen
- Surrounding bone may show variable osteoclastic and osteoblastic activity

## ANCILLARY TESTS

### Immunohistochemistry

- Large histiocytes stain S100 protein, CD68, and CD163 (+); CD1a, langerin, and BRAF (-)

## DIFFERENTIAL DIAGNOSIS

### Osteomyelitis

- RD should be distinguished from osteomyelitis by presence of characteristic histiocytes that stain for S100 protein and show emperipolesis
  - This distinction can be very difficult on small biopsy sample

### Langerhans Cell Histiocytosis

- Can be confused with RD since both contain S100(+) histiocytes but contains abundant eosinophils
- Histiocytes in Langerhans cell histiocytosis have more convoluted nuclei and express CD1a and langerin, which is not expressed in histiocytes in RD
- Unlike Langerhans cell histiocytosis, *BRAF* mutation is absent

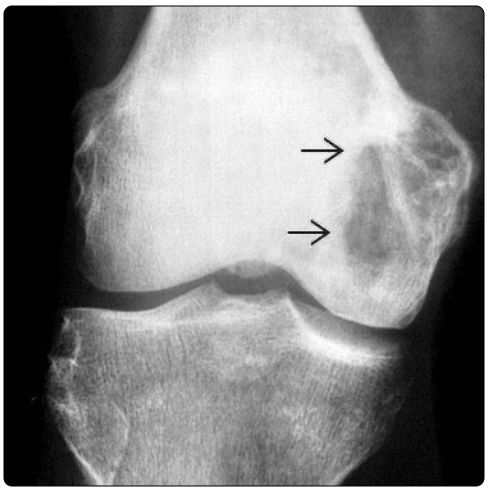
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**Lytic Mass in Humeral Head**



**Lytic Tumor With Sclerotic Margins**



**(Left)** *A frontal radiograph of the humerus in a patient with primary RD of the bone demonstrates a lytic lesion involving the proximal humerus extending to the subchondral region.* **(Right)** *An AP radiograph of the knee in a patient with RD of bone demonstrates a lytic lesion that appears to have arisen in the medullary cavity of the medial femoral condyle. There is a thick, but faintly seen, rim of reactive sclerosis at the bone margin.*

**Multiple Masses in Femur and Tibia**

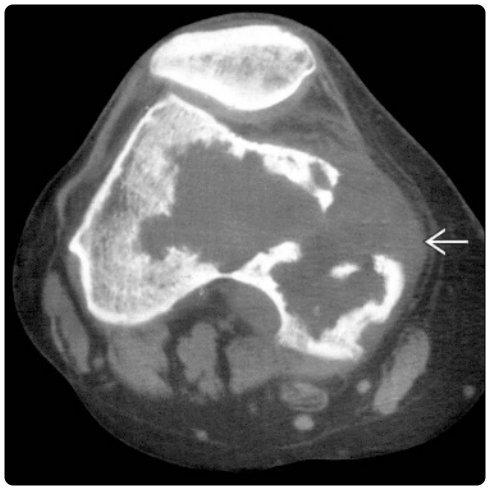


**Eccentric Lytic Mass**

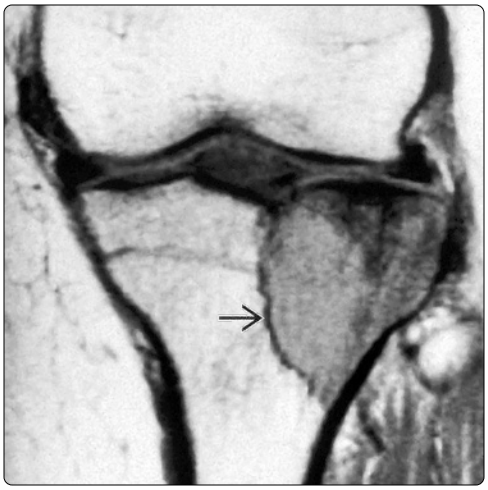


**(Left)** *In this coronal T1-weighted image of the knee, multiple round and oval low signal intensity masses are present. Each one consists of the inflammatory infiltrate characteristic of RD.* **(Right)** *An AP radiograph of RD involving the tibia shows a lytic lesion of the lateral tibial plateau extending into the metaphysis and with a thin rim of reactive sclerosis.*

**Destructive Mass**

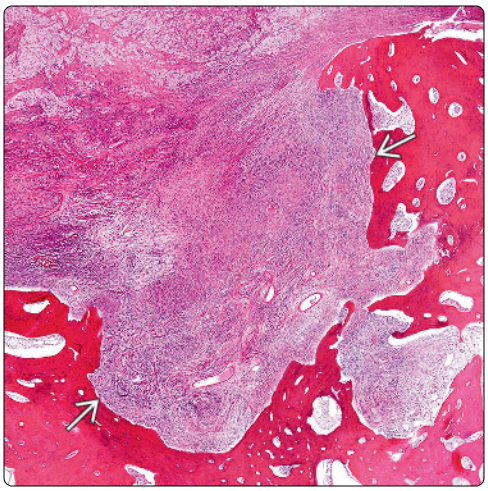


**Low Signal Intensity Mass**

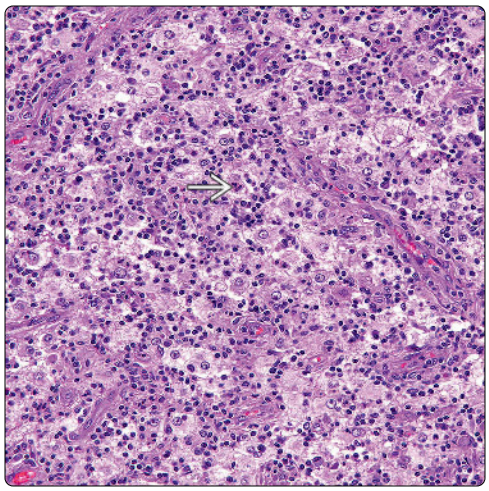


**(Left)** *Axial CT scan of primary intraosseous RD shows a lytic lesion involving the distal aspect of the femur that has broken through the cortex and extended into adjacent soft tissue. The adjacent bone is focally sclerotic.* **(Right)** *A T1-weighted MR shows the tibia in a patient with RD involving the lateral plateau. It contains areas of low signal suggesting either mineralization or engulfed preexisting cancellous bone. It is surrounded by a thin rim of very low signal, indicating reactive sclerosis.*

### Well-Circumscribed Margin

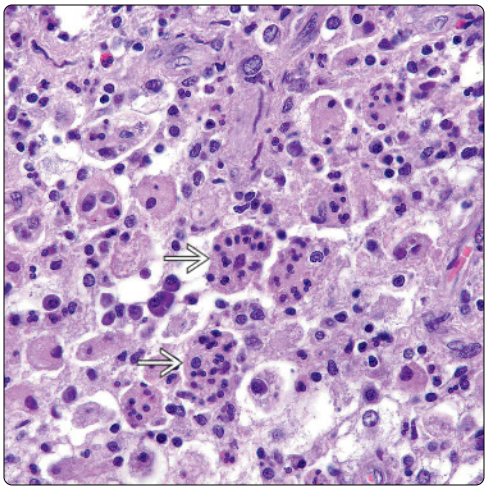


### Histiocytes and Inflammatory Cells

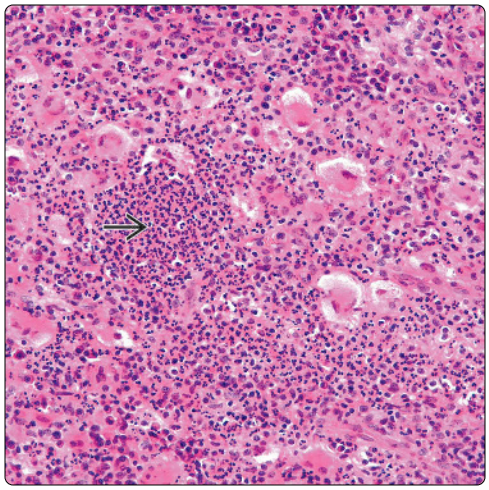


**(Left)** *RD may have a well-circumscribed margin. In this case, the lesion is sharply demarcated from the endosteal surface of the cortex* ⇒. **(Right)** *Medium-power view of primary intraosseous RD of the bone shows numerous histiocytes with finely granular, pale, eosinophilic cytoplasm admixed with an extensive inflammatory infiltrate. Emperipolesis is present* ⇒.

### Emperipolesis

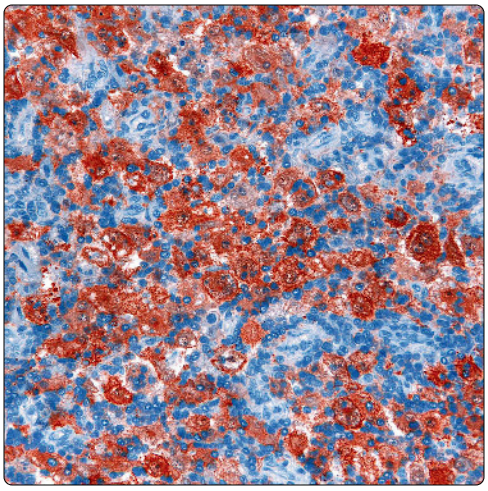


### Extensive Neutrophilic Infiltrate

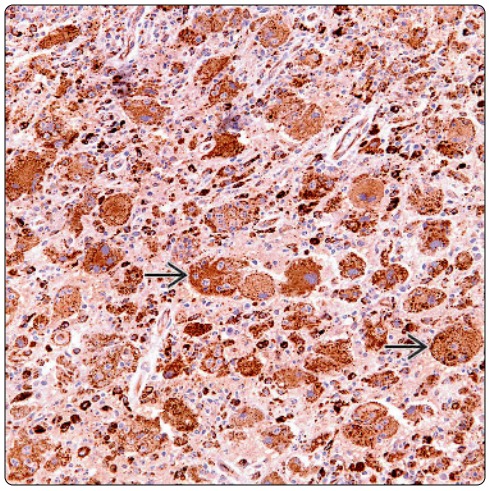


**(Left)** *Primary RD of the bone shows sheets of large histiocytes with finely granular eosinophilic cytoplasm and scattered inflammatory cells. Many inflammatory cells are present within the cytoplasm of the histiocytes (so-called emperipolesis)* ⇒, *which is a typical finding in RD.* **(Right)** *This RD of the bone mimics acute osteomyelitis. In addition to the large histiocytes, there is a dense acute inflammatory infiltrate with microabscesses* ⇨.

### S100



### CD68

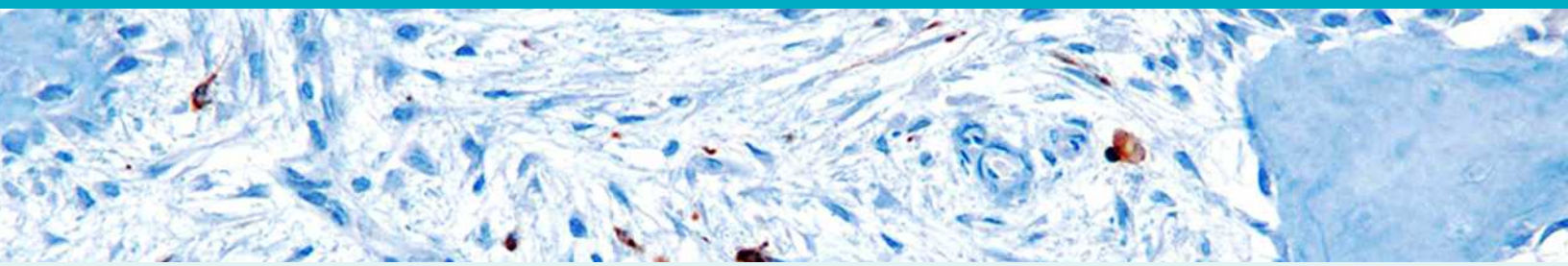


**(Left)** *In this primary intraosseous RD of the bone, the large histiocytes express S100 protein by immunohistochemical staining, typically seen in RD. The histiocytes do not stain for CD1a or langerin.* **(Right)** *Primary RD of the bone has been stained immunohistochemically for CD68. There is diffuse staining of the large histiocytes* ⇨ *and also some staining of the mononuclear cells in the background.*

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SECTION 13

# Miscellaneous Mesenchymal Tumors




| | |
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| Osteofibrous Dysplasia | **382** |
| Adamantinoma | **386** |
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| Myxopapillary Ependymoma | **414** |
| Phosphaturic Mesenchymal Tumor | **416** |

# Osteofibrous Dysplasia

KEY FACTS

## TERMINOLOGY

- Benign fibroosseous lesion of bone, which characteristically occurs during childhood and arises in anterior cortex of tibia or fibula

## CLINICAL ISSUES

- Develops during 1st and 2nd decades of life
- Restricted to anterior cortex of tibia &/or fibula

## IMAGING

- Single well-delineated lytic lesion but more commonly consists of multiple lytic foci scattered along anterior cortex of tibia

## MOLECULAR

- Mutations in *GNAS* gene are not detected

## MICROSCOPIC

- Trabeculae of woven bone are rimmed by prominent osteoblasts and scattered osteoclasts

## ANCILLARY TESTS

- Isolated single stromal cells express keratin

## TOP DIFFERENTIAL DIAGNOSES

- Well-differentiated adamantinoma
  - Distinguished from osteofibrous dysplasia by presence of clusters of keratin-positive epithelial cells in adamantinoma
- Fibrous dysplasia
  - Intramedullary lesion
- Classic adamantinoma
  - Epithelial component dominates this lesion, readily distinguishing it from osteofibrous dysplasia

## DIAGNOSTIC CHECKLIST

- May be impossible to distinguish between osteofibrous dysplasia and well-differentiated adamantinoma on limited biopsy specimens

**Osteofibrous Dysplasia of Tibia and Fibula**



*Plain radiograph of osteofibrous dysplasia shows multifocal lesions involving the tibia and fibula. Note the sclerotic margins. The lesions were confined to the cortex, a finding that is better appreciated on a CT scan.*

**Osteofibrous Dysplasia of Tibia**



*Plain radiograph shows a typical case of osteofibrous dysplasia arising in the midshaft of the tibia. The lesion shows a sclerotic margin with a lytic appearance in the center.*

## TERMINOLOGY

### Definitions

- Benign fibroosseous lesion of bone, which characteristically occurs during childhood and arises in anterior cortex of tibia or fibula

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Accounts for < 1% of all bone tumors
- Age
  - Develops during 1st and 2nd decades of life

### Site

- Restricted to tibia &/or fibula, typically mid shaft of anterior cortex

### Presentation

- Pain and localized swelling
- Bowing deformity
- Infrequently, pathologic fracture

### Natural History

- Gradual growth during 1st decade followed by stabilization in following decade
  - Majority undergo spontaneous regression after puberty
- Progression to well-differentiated adamantinoma has been shown in some cases
  - Progression to classic adamantinoma has not been reported

### Treatment

- Conservative approach is favored
- Surgery should be delayed as long as possible, preferably after puberty
  - May be indicated for growing or extensive lesions, pathologic fracture, or significant tibial bowing
  - Recurrences possible after surgery

## IMAGING

### Radiographic Findings

- Well-delineated lucency arising in cortex
- May manifest as single lytic lesion but more commonly consists of multiple lytic foci scattered along anterior cortex
- Surrounded by areas of sclerosis
- Overgrowth of affected cortex frequently results in anterior bowing

## MACROSCOPIC

### General Features

- Solid, yellow or white, gritty lesion
- Confined to cortex; cortex may be thinned, but periosteum remains intact

## MICROSCOPIC

### Histologic Features

- Irregular, curvilinear trabeculae of woven bone merging with preexisting peripheral lamellar cancellous bone
  - Trabeculae of woven bone are rimmed by prominent osteoblasts and scattered osteoclasts
- Intervening stroma composed of bland spindle cells embedded within collagenous matrix
- Zonation may be apparent with mature bony trabeculae at periphery of lesion

## ANCILLARY TESTS

### Immunohistochemistry

- Isolated single stromal cells express keratin
  - Clusters of epithelial cells, as seen in well-differentiated adamantinoma, are absent
- Basal-type keratin profile
  - Positive: Cytokeratins 14 and 19; negative: Cytokeratins 8 and 18

### Genetic Testing

- Unlike fibrous dysplasia, mutations in *GNAS* gene are not detected
- Germline mutations in *MET* are detected in hereditary forms of osteofibrous dysplasia

## DIFFERENTIAL DIAGNOSIS

### Well-Differentiated Adamantinoma

- Distinguished from osteofibrous dysplasia by presence of clusters of keratin-positive epithelial cells in adamantinoma
- Well-differentiated adamantinoma and osteofibrous dysplasia are closely related clinically, radiologically, and genetically
  - Shared features
    - Location in cortex of tibia or fibula
    - Histologically characterized by woven bone with osteoblastic rimming

### Classic Adamantinoma

- Epithelial component dominates this lesion, readily distinguishing it from osteofibrous dysplasia

### Fibrous Dysplasia

- Intramedullary lesion
- Bony trabeculae lack osteoblastic rimming
- ~ 1/2 of all cases of fibrous dysplasia show codon 201 *GNAS* mutations

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- May be impossible to distinguish between osteofibrous dysplasia and well-differentiated adamantinoma on limited biopsy specimens
  - Unresected patients with osteofibrous dysplasia should be closely followed clinically
    - Disease progression raises possibility that lesion is actually adamantinoma

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**Bowing of Tibia**

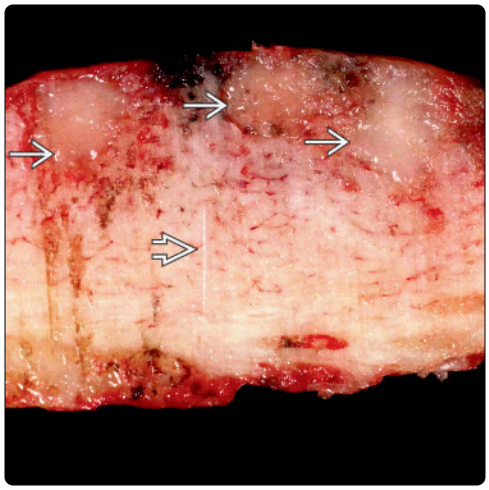


**Osteofibrous Dysplasia**

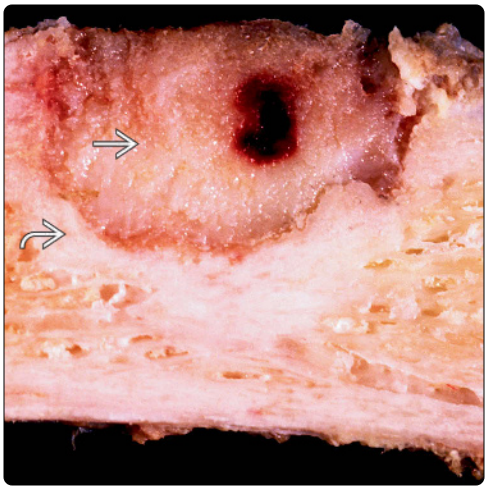


**(Left)** *Plain radiograph of a young child with osteofibrous dysplasia shows a large lytic lesion occupying the proximal 1/2 of the tibia. The lesion causes expansion of the tibia and bowing of the tibia and fibula. It is multiloculated and bounded posterolaterally by a thin sclerotic rim.* **(Right)** *Fluid-sensitive MR of osteofibrous dysplasia shows high signal intensity involving the mass in the tibial cortex.*

**Tumors Involving Tibial Cortex**

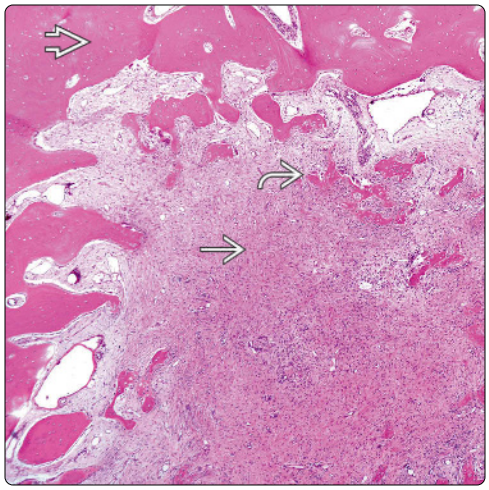


**Tumor With Sclerotic Rim**

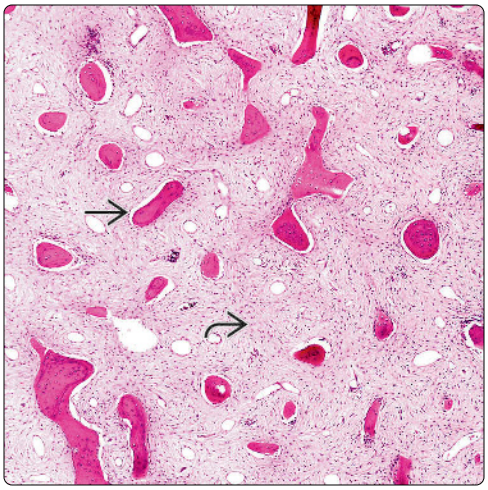


**(Left)** *Gross photograph of a resected tibia involved by osteofibrous dysplasia shows 3 intracortical lesions with a solid, gray-white appearance. The perilesional cortical bone is thickened and sclerotic. The lesion did not extend into the medullary canal.* **(Right)** *Gross photograph shows osteofibrous dysplasia. The intracortical lesion is composed of gritty, white tissue. The tumor is surrounded by a rim of sclerotic bone and is confined to the cortex.*

**Intracortical Tumor**

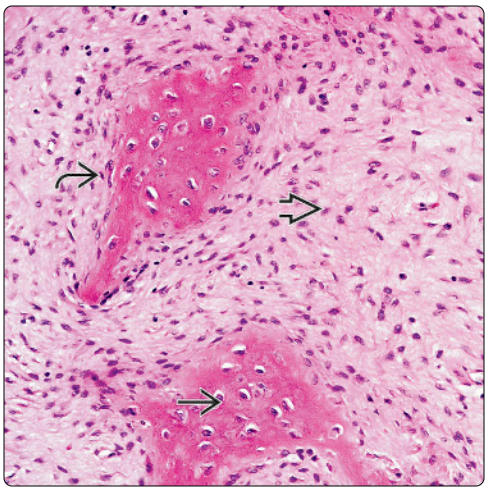


**Irregular Trabeculae of Woven Bone**

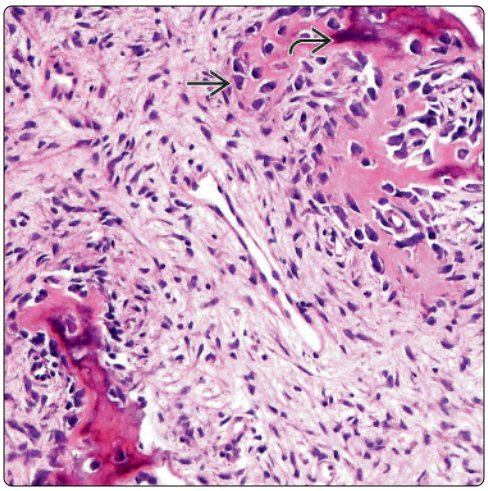


**(Left)** *Low-power H&E of osteofibrous dysplasia is shown. The lesion is surrounded by hyperostotic cortical bone. The lesional bony trabeculae are noted predominantly at the periphery of the lesion and merge with the cortical bone.* **(Right)** *H&E shows osteofibrous dysplasia composed of trabeculae of woven bone surrounded by a population of spindle-shaped cells. The trabeculae are pink and lack mineralization. The lesion does not infiltrate preexisting bone (not seen in this microphotograph).*

### Woven Bone and Tumor Cells

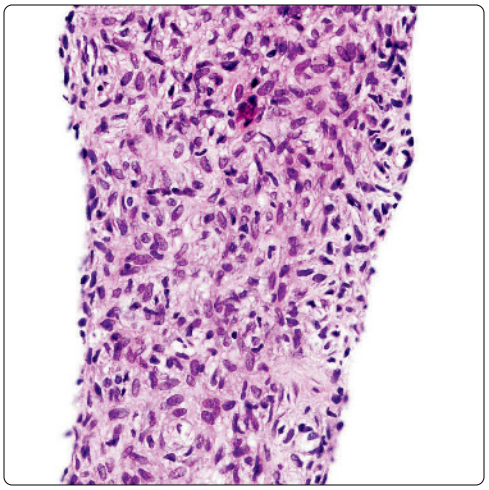


### Osteoblastic Rimming

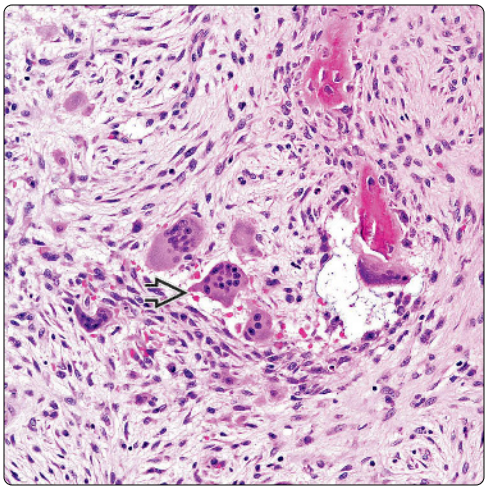


**(Left)** *The trabeculae of osteofibrous dysplasia are randomly arranged. Osteocytes are embedded within the osteoid matrix. The mesenchymal cells are monotonous and lack nuclear atypia.* **(Right)** *Osteofibrous dysplasia shows irregular bony trabeculae that are lined by prominent osteoblasts. The matrix is focally calcified, causing pink to purple trabeculae. The osteoblasts and intervening mesenchymal cells lack cellular atypia.*

### Needle Biopsy of Osteofibrous Dysplasia

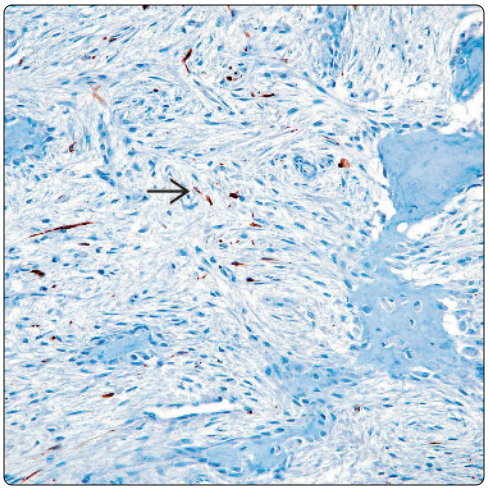


### Tumor With Osteoclast-Type Giant Cells

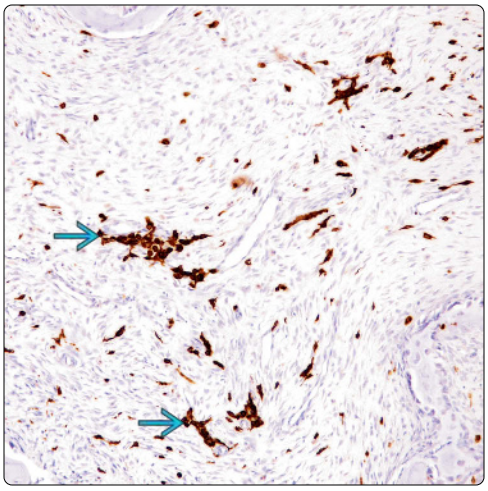


**(Left)** *A biopsy from a case of osteofibrous dysplasia is shown; trabeculae of woven bone were not represented. However, the intracortical location suggests either osteofibrous dysplasia or osteofibrous dysplasia-like adamantinoma.* **(Right)** *Osteofibrous dysplasia shows trabeculae of woven bone. Although osteoclast-type giant cells are seen, a giant cell tumor can be excluded because of the intracortical location of the lesion and the lack of similarity between the nuclei of the giant cells and those of the stromal cells.*

### Keratin-Positive Tumor Cells



### Aggregate of Keratin-Positive Cells



**(Left)** *Osteofibrous dysplasia shows scattered keratin-positive stromal cells. Clusters of keratin-positive epithelial cells are not seen. Clusters of keratin-positive cells would support a diagnosis of well-differentiated adamantinoma.* **(Right)** *Aggregates of keratin-positive cells, as seen in this image, are characteristic of a well-differentiated adamantinoma. Osteofibrous dysplasia would show only single isolated keratin-positive cells.*

# Adamantinoma

KEY FACTS

## TERMINOLOGY

- Low-grade biphasic malignant tumor of bone composed of epithelial and stromal elements

## CLINICAL ISSUES

- Almost exclusively in tibia ± involvement of fibula
- Wide surgical excision with reconstructive surgery
- Metastases usually develop after long clinical course
- Virtually all metastatic lesions are classic adamantinoma (ADA)
- Poor prognostic factors: Male sex, short duration of symptoms, pain, and inadequate initial treatment
- Very uncommon; < 1% of primary bone malignancies
- Classic ADA affects patients > 20 years
- Well-differentiated ADA affects patients < 20 years

## IMAGING

- Well-circumscribed intracortical lytic foci showing characteristic soap bubble appearance

## MACROSCOPIC

- Intracortical lesion
- Soft/gritty, red-tan, well circumscribed
- Varies from < 1 cm to > 10 cm

## MICROSCOPIC

- Epithelial and osteofibrous dysplasia-like areas
- Classic ADA: Epithelial component is prominent
- In well-differentiated ADA, osteofibrous dysplasia-like area is predominant
- Epithelial cells are keratin and p63 positive

## TOP DIFFERENTIAL DIAGNOSES

- Osteofibrous dysplasia
  - Lacks epithelial cell aggregates
- ADA-like Ewing sarcoma
  - Demonstrates t(11;22)
  - Contains malignant round cells

**Large Bubbly Tumor**



*AP radiograph shows a large, well-differentiated adamantinoma that presents as bubbly, lucent areas. The lesions are geographic with thick, sclerotic reactive margins. Some of the lesions are eccentric, expand the bone, and are delineated by a shell of reactive bone.*

**Tan-White Tumor**



*This is a resected well-differentiated adamantinoma of the tibia that involves the medullary cavity, cortex, and surface of the bone. The tumor is tan-white and nodular.*

## TERMINOLOGY

### Abbreviations

- Adamantinoma (ADA)

### Definitions

- Low-grade biphasic malignant neoplasm of bone, composed of epithelial and mesenchymal elements

## ETIOLOGY/PATHOGENESIS

### Unknown

- Controversial but likely epithelial cell origin

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Very uncommon; < 1% of primary bone malignancies
- Age
  - Classic ADA affects patients > 20 years
  - Well-differentiated ADA affects patients < 20 years
- Sex
  - More common in males

### Site

- Almost exclusively in tibia ± involvement of fibula
- Both types may be confined to cortex
  - Well-differentiated ADA usually exclusively involves cortex but may extend into medullary cavity
  - Classic type may have soft tissue extension

### Presentation

- Pain; palpable mass
- Anterior bowing deformity
- Symptoms often noted for years prior to diagnosis

### Treatment

- Surgery with wide excision and reconstruction

### Prognosis

- Well-differentiated ADA: Local recurrence
- Classic ADA: Metastases may develop after long clinical course in 12-29% of patients
  - All metastatic lesions are classic ADA
- Most common site of spread is lung
- Poor prognostic factors: Male sex, short duration of symptoms, pain, and inadequate initial treatment

## IMAGING

### Radiographic Findings

- Diaphyseal, well-circumscribed intracortical lytic foci with soap bubble appearance
- Adjacent cortex is irregularly thickened and sclerotic
- Multiple discrete lytic foci separated by normal or sclerotic bone

### MR Findings

- Solitary or multiple small nodules with low signal intensity on T1-weighted images
- High signal intensity on T2-weighted images
- Enhancement with gadolinium

### CT Findings

- Shows cortical origin of lesion; sclerotic margins

## MACROSCOPIC

### General Features

- Bowing deformity may be present
- Soft/gritty, red-tan, well-circumscribed, intracortical tumor surrounded by sclerotic bone
- May be multifocal with normal intervening bone
- Classic variant is tan-white and can involve medullary canal and soft tissue

### Size

- Varies from < 1 cm to > 10 cm

## MICROSCOPIC

### Histologic Features

- Classic ADA
  - Epithelial component prominent, while osteofibrous dysplasia-like areas are inconspicuous
  - Epithelial cells have 4 morphological patterns
    - Basaloid: Nests of spindle cells surrounded by palisading basal cells
    - Spindle: Spindle cells arranged in intersecting fascicles resembling fibrosarcoma
    - Tubular: Gland-like spaces lined by 1 or more layers of cuboidal or flattened cells
    - Squamoid: Nests of epithelial cells with keratinization
- Well-differentiated ADA
  - Predominance of osteofibrous dysplasia-like areas
    - Woven bone with osteoblastic rimming
  - Small epithelial nests present; may be inconspicuous

## ANCILLARY TESTS

### Immunohistochemistry

- Epithelial cells are keratin positive and have profile similar to basal layer cells of epidermis
- Epithelial cells also express p63

## DIFFERENTIAL DIAGNOSIS

### Osteofibrous Dysplasia

- Lacks aggregates of epithelial cells

### Adamantinoma-Like Ewing Sarcoma

- Malignant round cell tumor with rearrangement of *EWSR1*

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Epithelial nests in well-differentiated ADA are small and easily confused with small vessels
  - Keratin confirms their epithelial nature

## SELECTED REFERENCES

1. Bethapudi S et al: Imaging in osteofibrous dysplasia, osteofibrous dysplasia-like adamantinoma, and classic adamantinoma. Clin Radiol. 69(2):200-8, 2014
2. Keeney GL et al: Adamantinoma of long bones. A clinicopathologic study of 85 cases. Cancer. 64(3):730-7, 1989

### Tumors in Tibia and Fibula



### Intracortical Masses



**(Left)** *Well-differentiated adamantinoma presenting as mixed lucent and sclerotic lesions involves the medullary space and cortex of the midshaft of the tibia and fibula that deforms the bones.* **(Right)** *Well-differentiated adamantinoma usually shows significant involvement of the tibial cortex. The tumor often presents as multiple tan, intracortical ➔ nodules that induce subperiosteal reactive bone.*

### Bowing of Tibia



### Distorted Tibia



**(Left)** *In this lateral radiograph of a 2-year-old child, there is a well-differentiated adamantinoma that produces a well-circumscribed lytic tumor involving the cortex and medullary cavity of the tibia. The tumor has resulted in bowing of the tibia.* **(Right)** *This is the accompanying sagittal T2WI MR to the lateral radiograph of the well-differentiated adamantinoma. The tumor involves the cortex and medullary cavity ➔ and has distorted the tibia, which is bowed.*

### Elongate Mass

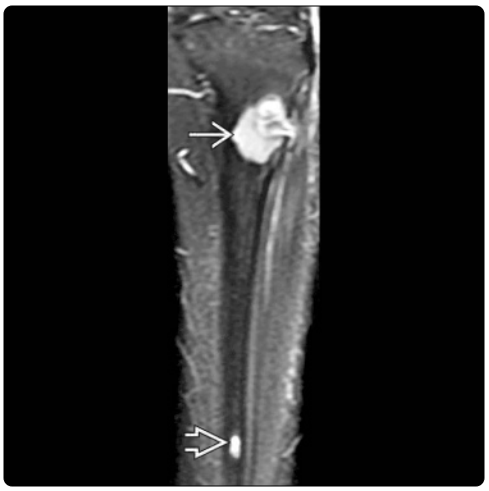


### Bright Tumor



**(Left)** *Sagittal T1WI MR shows a well-differentiated adamantinoma that manifests as a well-defined mass that involves the cortex and marrow. The mass ➔ is iso- to slightly hyperintense compared to muscle and spreads along the anterior cortex. The abutting marrow ⇨ is unremarkable.* **(Right)** *MR of a well-differentiated adamantinoma centered in the diaphysis of the tibia shows enhancement ⇨ with gadolinium. A smaller, proximal lesion ➔ is connected along the anterior cortex.*

### Multiple Tumors



### Intracortical Mass

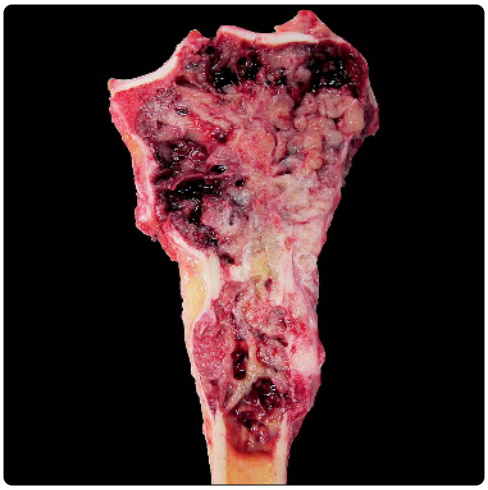


**(Left)** *Coronal fat-saturated T1WI MR of a classic adamantinoma is lobulated, enhancing, and focally expands the cortex. A smaller, enhancing, well-differentiated adamantinoma is present in the distal shaft.* **(Right)** *Axial CT of a classic adamantinoma shows a geographic, cortically based mass that deforms the tibia. The tumor is isodense with skeletal muscle and bulges into the soft tissue. The internal margin is sharp and sclerotic.*

### Large Destructive Tumor

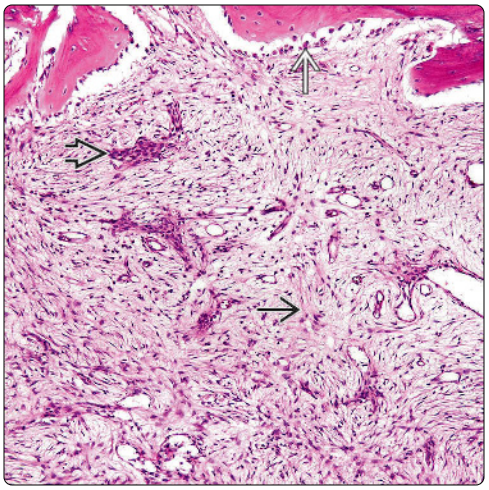


### Hemorrhagic Lobulated Mass

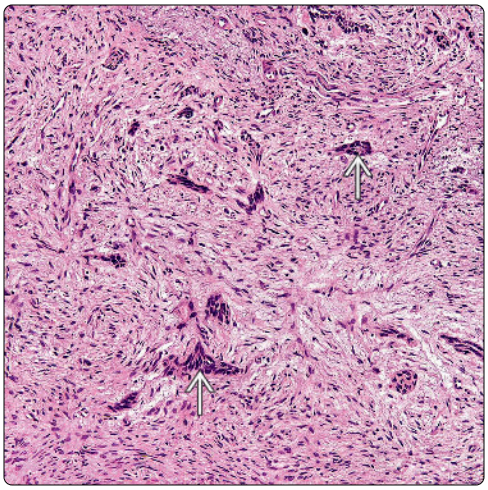


**(Left)** *This classic adamantinoma presents as a large, lytic, poorly defined destructive mass. The tumor extends from the diaphysis into the epiphysis and has breached the cortex in several areas and grows into the soft tissues.* **(Right)** *This is the gross specimen of the tumor shown in the accompanying plain film. The hemorrhagic, tan-white tumor fills the medullary cavity of the proximal tibia and erodes the cortex and extends into the soft tissues.*

### Small Nests of Epithelium

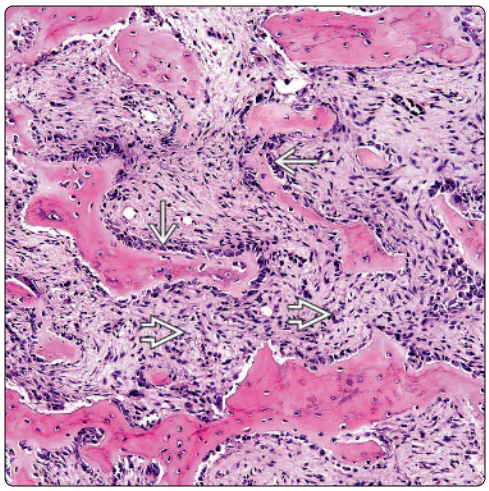


### Prominent Spindle Cell Stroma

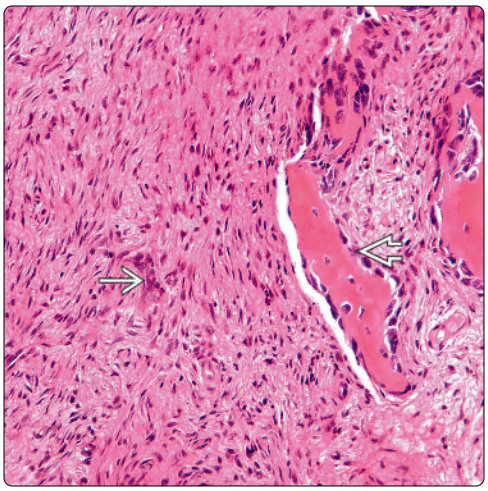


**(Left)** *Well-differentiated adamantinoma contains a prominent fibrous-appearing stroma with scattered islands of epithelial cells. Also present are irregular trabeculae of reactive woven bone lined by prominent osteoblasts that is reminiscent of osteofibrous dysplasia.* **(Right)** *Abundant fibrous stroma and small islands of epithelial cells are characteristic of well-differentiated adamantinoma. The stromal spindle cells are often arranged in a storiform pattern.*

**Osteoblastic Rimming**

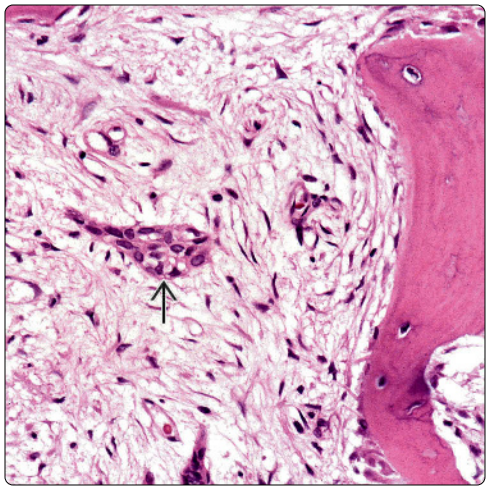


**Small Epithelial Nest**

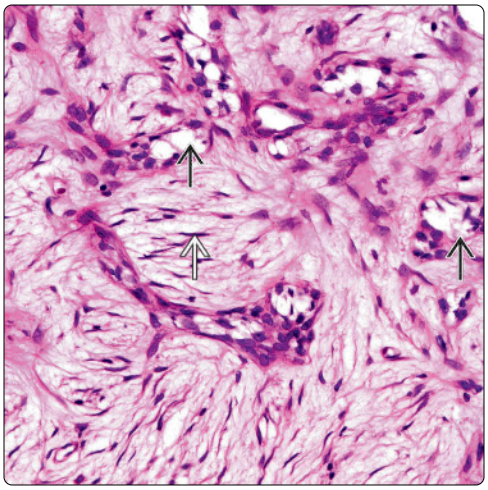


**(Left)** *Well-differentiated adamantinomas have areas that are osteofibrous dysplasia-like in appearance. They have irregular trabeculae of woven bone rimmed by plump osteoblasts and fibrous-appearing stroma.* **(Right)** *Well-differentiated adamantinoma can be confused with osteofibrous dysplasia and fibrous dysplasia. Small islands of epithelial cells surrounded by abundant fibrous-appearing stroma and trabeculae of woven bone lined by osteoblasts are characteristic.*

**Island of Epithelium**

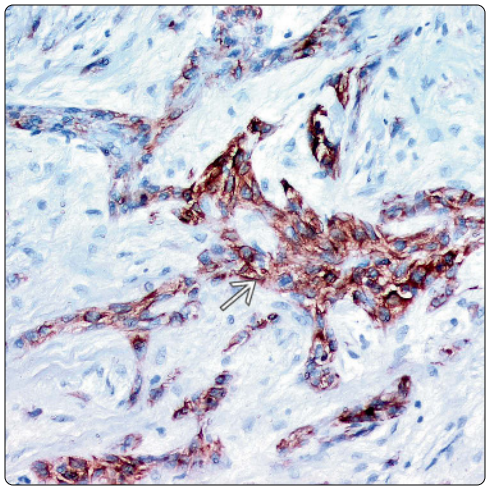


**Spindle and Tubular Patterns**

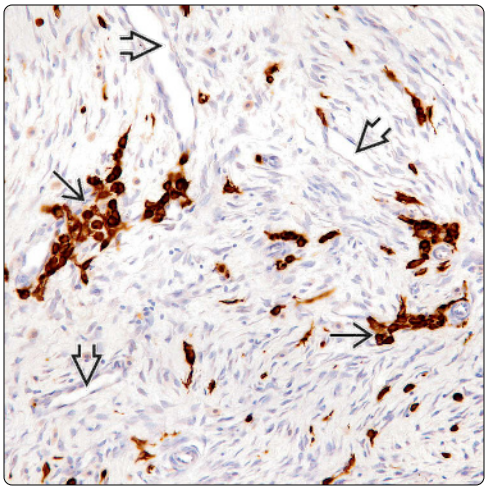


**(Left)** *A small island of epithelium is surrounded by fibrous stroma in a well-differentiated adamantinoma. The epithelial cells are cytologically bland and do not demonstrate mitotic activity.* **(Right)** *Cords and islands of epithelium in a well-differentiated adamantinoma have a tubular pattern, which can mimic blood vessels. Both the epithelium and the spindle cells in the fibrous-appearing stroma are cytologically banal and lack mitoses.*

**Keratin Staining Epithelial Cells**

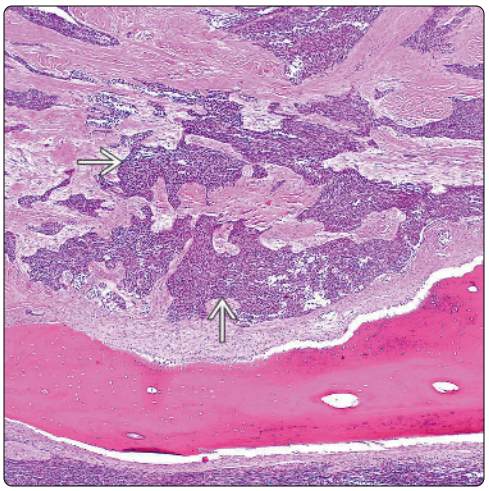


**Multiple Keratin-Positive Nests of Cells**

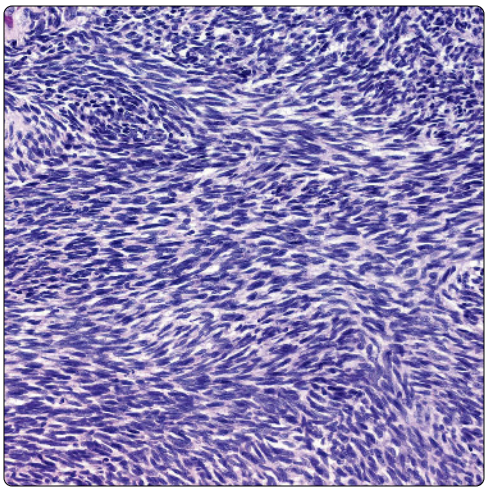


**(Left)** *The epithelial islands in well-differentiated adamantinoma stain strongly with keratin. This stain can help accentuate their presence.* **(Right)** *A keratin stain highlights the presence of scattered epithelial islands in well-differentiated adamantinoma. Note that individual spindle cells are also positive. The endothelial lining of vascular spaces are negative for this marker.*

### Large Areas of Epithelium



### Spindle Cell Pattern

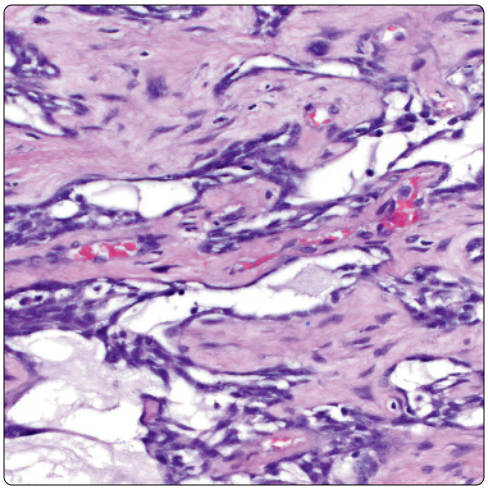


**(Left)** *Classic adamantinoma has caused resorption of the cortex and grows into the soft tissues and medullary cavity. The cellular tumor appears as multiple irregular islands ➡ of sheets of cells, which are delineated by reactive fibrous tissue.* **(Right)** *Classic adamantinoma is a densely cellular neoplasm that may demonstrate different patterns, including spindled, basaloid, tubular, and squamous. In this spindled variant, the tumor cells are arranged in intersecting fascicles.*

### Basaloid Pattern

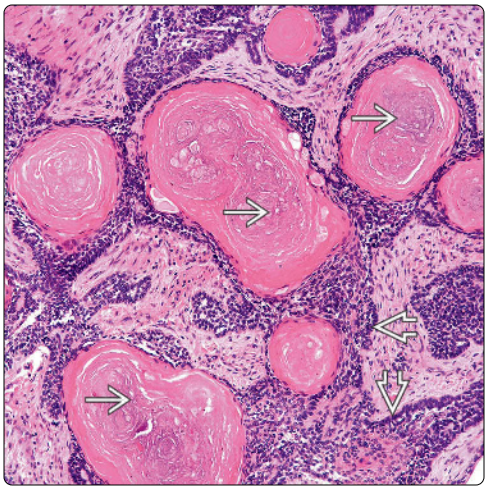


### Tubular Pattern

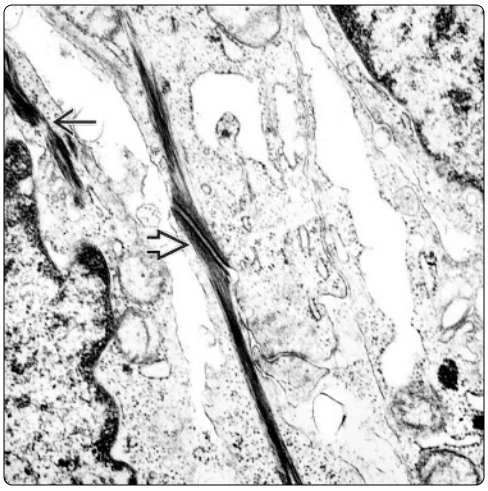


**(Left)** *Epithelial island ⇨ in classic adamantinoma is surrounded by collagenous-appearing stroma. The tumor cells in the center ➡ of the island are spindle-shaped and those at the periphery palisade in a basaloid fashion.* **(Right)** *In classic adamantinoma, some of the epithelial cells can form tubular structures that mimic blood vessels as they course through the fibrous stroma.*

### Squamous Differentiation



### Intercellular Junctions



**(Left)** *The rarest variant of classic adamantinoma is the squamous pattern in which the centers of the epithelial islands show obvious keratinization ➡. The remaining portions of the epithelial islands may be spindled or basaloid ➡.* **(Right)** *Ultrastructurally, the epithelial cells in an adamantinoma are cohesive, have a moderate amount of cytoplasm, and are joined by desmosome-like junctions ⇨. One of the cells has intracytoplasmic aggregates of tonofilaments ⇨.*

KEY FACTS

## TERMINOLOGY

- **Lipoma**
  - Benign neoplasm of mature adipocytes
- **Hibernoma**
  - Benign neoplasm showing brown fat differentiation
- **Liposarcoma**
  - Extremely rare malignant neoplasm with phenotype that recapitulates fat

## CLINICAL ISSUES

- **Lipoma**
  - Prognosis excellent, rarely recurs
- **Liposarcoma**
  - Generally, behavior of tumor correlates with its histologic grade

## IMAGING

- **Lipoma**
  - Intramedullary lipoma usually produces well-defined lytic mass surrounded by thin rim of sclerosis
- **Liposarcoma**
  - May be either well delineated or poorly defined and aggressive in appearance

## MICROSCOPIC

- **Lipoma**
  - Consists of lobules of mature-appearing white adipocytes that may replace marrow and encase preexisting bony trabeculae
- **Hibernoma**
  - Composed of aggregates of brown fat cells with granular eosinophilic cytoplasm and central nuclei
- **Liposarcoma**
  - Different types of liposarcoma arising in bone have histologic features similar to their soft tissue counterparts

**Radiograph of Lipoma of Calcaneus**



*A radiographic image of an intraosseous lipoma demonstrating a lucent lesion in the calcaneus with well-defined margins. Some internal trabeculations are visible.*

**MR of Intraosseous Lipoma**



*This axial MR PD sequence of an intraosseous lipoma of the calcaneus shows the internal signal intensity of the lesion to be similar to marrow fat for most of the area with a central area of cystic changes.*

## TERMINOLOGY

### Abbreviations

- **Liposarcoma**
  - Well-differentiated liposarcoma
  - Myxoid/round cell liposarcoma

### Synonyms

- Intramedullary lipoma
- Intracortical lipoma
- Ossifying lipoma
- Parosteal lipoma

### Definitions

- **Lipoma**
  - Benign neoplasm of mature adipocytes
  - When involving bone, may arise within bone, cortex, or on its surface (parosteal)
- **Hibernoma**
  - Benign neoplasm showing brown fat differentiation
- **Liposarcoma**
  - Extremely rare primary malignant neoplasm of bone with phenotype that recapitulates fat

## ETIOLOGY/PATHOGENESIS

### Neoplasm

- Etiology is unknown for lipoma and liposarcoma
- No predisposing factors are known

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - **Lipoma** of bone
    - Intraosseous lipomas are uncommon
    - Account for < 0.1% of primary bone tumors
  - **Hibernoma** of bone
    - Very rare
    - Much more common in soft tissues
    - Only few cases have been reported in literature
  - **Liposarcoma** of bone
    - Very rare
    - Most cases are in form of single case reports
    - Much more common for soft tissue liposarcoma, especially myxoid liposarcoma, to metastasize to bone
- Age
  - **Lipoma**
    - Intraosseous lipomas occur over wide age range
    - Usually in 2nd-8th decades of life
    - Most patients are ~ 40 years old at time of diagnosis
    - Parosteal lipoma usually develops during adulthood
      - Most patients in 5th-6th decades of life at time of diagnosis
  - **Hibernoma**
    - Middle age to older individuals
  - **Liposarcoma**
    - Occurs in all age groups
    - Majority of patients are adults
- Sex
  - **Lipoma**
    - Intraosseous lipoma affects males more frequently than females
    - Parosteal lipoma also has slight male predominance
  - **Hibernoma**
    - More common in females
  - **Liposarcoma**
    - Slightly more common in males

### Site

- **Lipoma**
  - Vast majority of intraosseous lipomas are intramedullary
    - Usually arise in metaphyseal regions of long tubular bones
  - Frequently arise in femur, tibia, fibula, and calcaneus
  - Have also been described in pelvis, vertebrae, sacrum, skull, mandible, maxilla, and ribs
  - Rare cases are intracortical in origin
  - Parosteal lipoma generally develop on diaphyseal surface of long tubular bones
    - Usually femur, humerus, and tibia
- **Hibernoma**
  - Usually axial skeleton with ilium being the most common location
- **Liposarcoma**
  - Usually develops in long tubular bones
    - Most commonly tibia and femur
  - Can arise in diaphysis, metaphysis, or epiphysis

### Presentation

- **Lipoma**
  - May be asymptomatic and found incidentally
  - Can be painful
  - May be detected as visible or palpable mass
  - Rarely presents with pathologic fracture
- **Hibernoma**
  - Asymptomatic
  - Discovered incidentally on images taken for other reasons
- **Liposarcoma**
  - Painful mass

### Prognosis

- **Lipoma**
  - Excellent
  - Rarely recurs
- **Liposarcoma**
  - Generally, behavior of tumor correlates with its histologic grade
  - Well-differentiated liposarcoma has best prognosis
  - Pleomorphic liposarcoma has worst prognosis

## IMAGING

### Radiographic Findings

- **Lipoma**
  - Intramedullary lipoma usually produces well-defined lytic mass
    - Surrounded by thin rim of sclerosis
  - Lesion may also contain bony trabeculations or central calcifications
  - Bony expansion may occur in small caliber bones

- Parosteal tumors manifest as mass adjacent to cortical surface that may be thickened by periosteal reactive bone
  - May mimic osteochondroma radiographically
- Frequently associated with prominent ossification
- When arising in calcaneus, radiographic findings are very similar to so-called calcaneal cyst (simple bone cyst of calcaneus)

- **Hibernoma**
  - Presents as sclerotic lesion
- **Liposarcoma**
  - May be either well delineated or poorly defined and aggressive in appearance

### MR Findings

- **Lipoma**
  - Fat has high signal intensity on both T1- and T2-weighted sequences
    - Same signal characteristics as normal fat

### CT Findings

- **Lipoma**
  - Demonstrates fatty component with low density similar to fat
  - Like plain radiographs, may demonstrate central calcifications caused by fat necrosis and dystrophic calcifications

## MACROSCOPIC

### General Features

- **Lipoma**
  - Well defined
  - Soft
  - Yellow; similar to soft tissue lipoma
  - Some cases contain gritty spicules of bone or firm nodules of cartilage at base or scattered throughout mass
- **Liposarcoma**
  - Well-differentiated liposarcoma
    - Large
    - Lobulated
    - Yellow cut surface
  - Myxoid/round cell liposarcoma
    - Myxoid and gelatinous cut surface
  - Pleomorphic liposarcoma
    - May be yellow, grossly mimicking fatty neoplasm
    - May also be predominantly solid, mimicking high-grade sarcoma

## MICROSCOPIC

### Histologic Features

- **Lipoma**
  - Consists of lobules of mature-appearing adipocytes that may replace marrow and encase preexisting bony trabeculae
  - Each adipocyte contains single large, clear, cytoplasmic vacuole displacing crescent-shaped nucleus to periphery
  - Some tumors may demonstrate fat necrosis with foamy histiocytes and fibrosis
  - Ossifying lipomas contain delicate trabeculae of woven and lamellar bone that may be present throughout tumor
  - Some cases contain bone &/or nodules of hyaline cartilage in base or randomly sprinkled throughout mass
- **Hibernoma**
  - Composed of aggregates of brown fat cells with granular eosinophilic cytoplasm and central nuclei
- **Liposarcoma**
  - Different types of liposarcoma arising in bone have similar histologic features to their soft tissue counterparts
    - This includes well-differentiated, myxoid, and pleomorphic liposarcomas
  - Well-differentiated liposarcoma
    - Consists of sheets of mature-appearing white adipocytes with scattered tumor cells having enlarged hyperchromatic and irregular nuclei
    - Scattered lipoblasts may be present; they are distinguished by cytoplasmic vacuoles that are round, clear, and scallop nucleus
  - Myxoid/round cell liposarcoma
    - Consists of mildly atypical, oval, and spindle-shaped cells enmeshed in myxoid stroma; round cell liposarcoma composed predominantly of round cells
    - Contain finely arborizing vascular tree that has plexiform pattern
    - Lipoblasts are scattered throughout tumor
  - Pleomorphic liposarcoma
    - Characterized by sheets of large pleomorphic cells in which cytoplasm is either eosinophilic or filled with round clear vacuoles
    - Mitoses are usually numerous
    - Cytoplasm of neoplastic cells contains membrane-bound lipid droplets of varying size

## ANCILLARY TESTS

### Immunohistochemistry

- **Lipoma**
  - Neoplastic fat expresses S100 protein, similar to extraskeletal lipomas
- **Hibernoma**
  - Brown fat cells stain for S100 protein
- **Liposarcoma**
  - Well-differentiated liposarcoma stains for MDM2 and CDK4
  - Mature adipocytes stain for S100 protein

### Genetic Testing

- **Lipoma**
  - t(3;12)(q28;q14) and associated fusion transcript HMGIC-LPP, characteristic of subcutaneous lipoma, has been detected in 1 case of parosteal lipoma
- **Hibernoma**
  - Structural rearrangements of 11q13-21
- **Liposarcoma**
  - Well-differentiated liposarcoma contains giant ring chromosomes and supernumerary ring chromosomes
    - This leads to amplification of MDM2 and CDK4
  - Myxoid and round cell liposarcoma shows t(12;16) in 90% of tumors

- Leads to fusion of *DDIT3* (CHOP) and *FUS* (TLS) genes
- Rare cases show t(21;22)

### Electron Microscopy

- Lipoma
  - Show adipocytes with intracytoplasmic lipid droplets
- **Hibernoma**
  - Cells contain fat droplets in addition to numerous intracytoplasmic mitochondria
- **Liposarcoma**
  - Ultrastructurally, neoplastic cells contain intracytoplasmic, membrane-bound lipid droplets, nonmembrane-bound glycogen, dilated, rough endoplasmic reticulum, mitochondria, and basal lamina

## DIFFERENTIAL DIAGNOSIS

### DDx of Lipoma

- Bone infarcts
  - May have areas of calcifications similar to intraosseous lipoma
    - Calcifications have characteristic chimney smoke appearance radiographically
- Enchondroma
  - Well-circumscribed lytic with areas of mineralization similar to intraosseous lipoma radiographically
    - Pattern of mineralization different than in intraosseous lipoma in radiographs
- Osteochondroma
  - Can simulate parosteal lipoma radiographically
  - Easy to distinguish histologically
- Unicameral bone cyst
  - Especially unicameral bone cysts arising in calcaneus
  - With time, fat can accumulate in bone surrounding unicameral calcaneal cyst and radiographically it can be difficult to distinguish it from lipoma that has undergone cystic change

### DDx of Hibernoma

- Granular cell tumor
  - Has not been reported to arise in bone
- Adult rhabdomyoma
  - Soft tissue tumor that does not involve bone
- Myxoid liposarcoma
  - Myxoid liposarcoma can sometimes contain areas of brown fat differentiation
  - Very uncommon primary bone tumor

### DDx of Liposarcoma

- Atrophic marrow fat can simulate myxoid liposarcoma

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- **Lipoma**
  - When "normal" fat in curettage specimen is seen, think intraosseous lipoma
- **Hibernoma**
  - When you see brown fat cells on biopsy think of intraosseous hibernoma
- **Liposarcoma**
  - Vast majority of liposarcomas involving bone (especially myxoid liposarcoma) represent metastatic disease to bone and not primary neoplasm

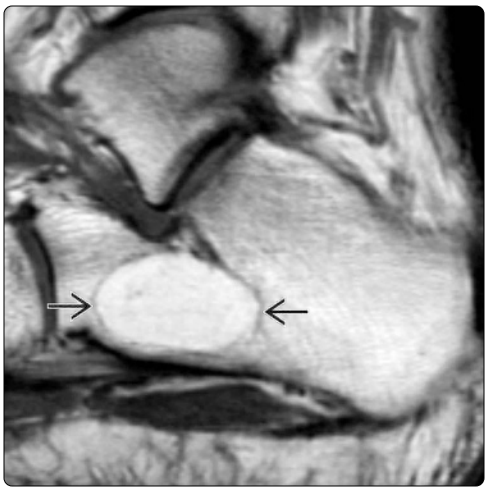
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**Radiograph of Intraosseous Lipoma**



**MR of Intraosseous Lipoma**

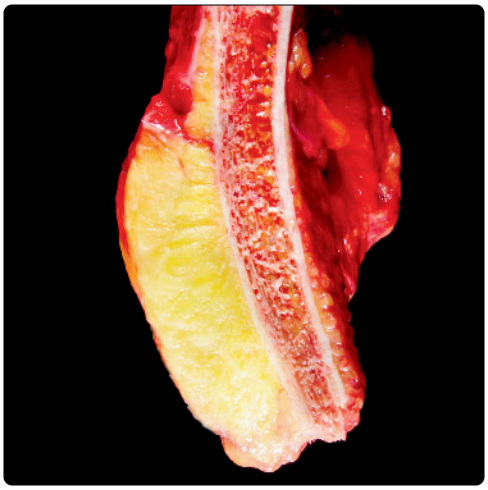


**(Left)** *An intraosseous lipoma ➡ arising in the calcaneus. The tumor is well defined and lucent with paucity of trabeculations.* **(Right)** *An axial PD sequence of an intraosseous lipoma of the calcaneus ⇨ shows the internal signal intensity of the lesion to be similar to marrow fat for most of the area with dark signal areas representing some internal septations.*

**CT of Parosteal Lipoma**



**Gross Photograph of Parosteal Lipoma**

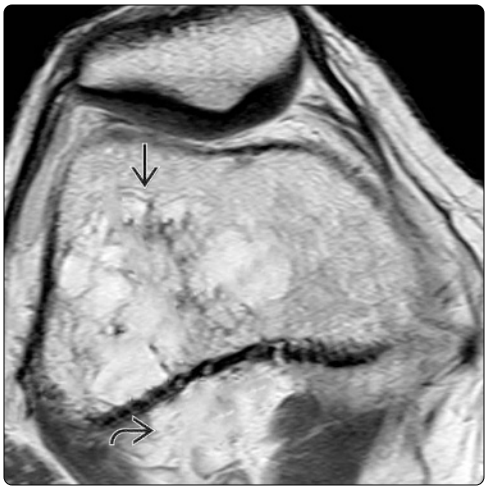


**(Left)** *An axial CT scan of a parosteal lipoma ➡ shows a low-density mass arising on the surface of the rib and involving the paraspinal soft tissues of the thoracic spine. The density of the tumor is similar to subcutaneous fat. The linear densities within the mass represent septations.* **(Right)** *This surface lipoma shows a well-circumscribed, lobulated, bright yellow mass arising on the surface of the rib (parosteal lipoma). The underlying cortex is intact and there is no involvement of the underlying bone.*

**Radiograph of Intraosseous Lipoma**



**MR of Intraosseous Lipoma**

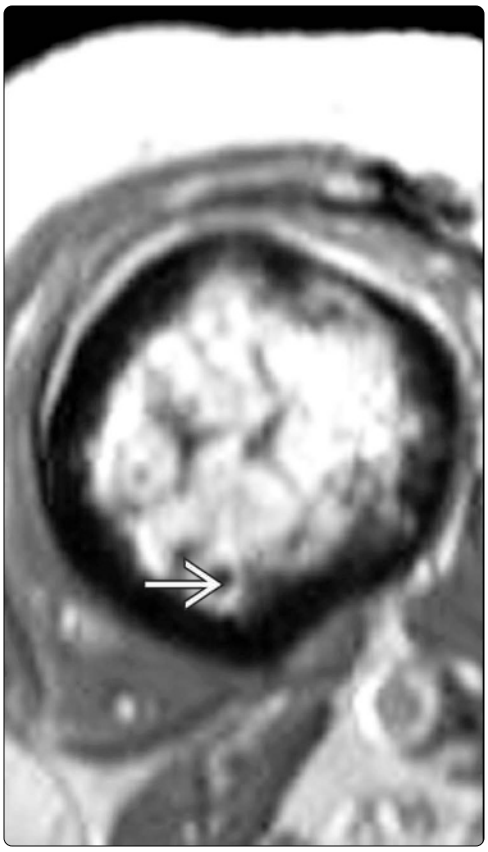


**(Left)** *A radiograph of an intraosseous lipoma ⇨ of the distal femur demonstrates a lesion within the distal femur with thick, dense margins. The lesion extends from the metaphysis to the subarticular bone.* **(Right)** *This axial PD MR of an intraosseous lipoma ⇨ of the distal femur demonstrates a multilobulated lesion with fat signal intensity. The lesion extends to the posterior soft tissues ⇨.*

Calcified Intraosseous Lipoma

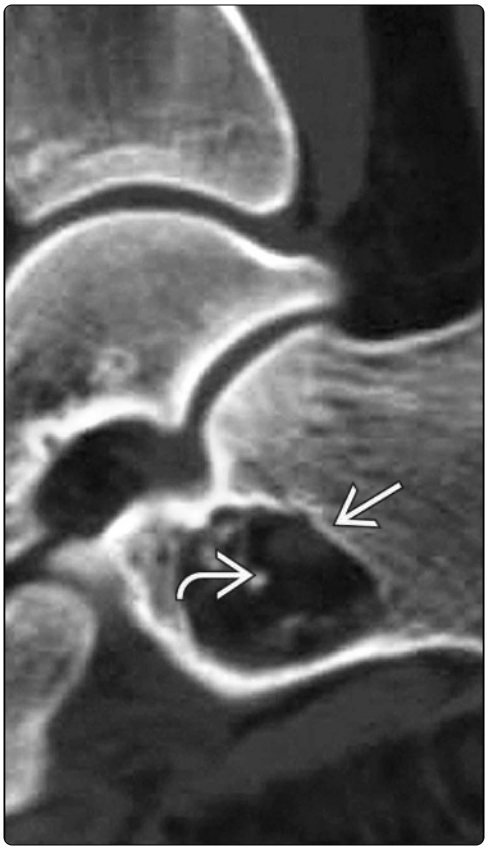


MR of Intraosseous Lipoma



**(Left)** *Radiograph of an intraosseous lipoma arising in the diaphysis of the femur shows an intramedullary lesion that has expanded the distal femoral cortex and contains ring-shaped calcific densities corresponding to areas of fat necrosis and dystrophic calcifications.* **(Right)** *Axial T1-weighted MR of an intraosseous lipoma shows that the tumor contains the signal characteristics similar to subcutaneous fat. The linear and round dark signal foci represent septations and calcifications.*

Intraosseous Lipoma of Calcaneus



Metastatic Myxoid Liposarcoma to Bone



**(Left)** *This radiographic view of an intraosseous lipoma of the calcaneus demonstrates a lucent lesion arising within the medullary cavity with dystrophic calcifications. The tumor is well demarcated and is surrounded by a thin, sclerotic rim of bone.* **(Right)** *Primary liposarcoma of bone is extremely rare. It is more common for liposarcoma to metastasize to bone. This is a gross image of a metastatic myxoid liposarcoma to the femur. The tumor is myxoid and cystic and involves the proximal diaphysis extending all the way to the distal metaphysis.*

### Intraosseous Lipoma

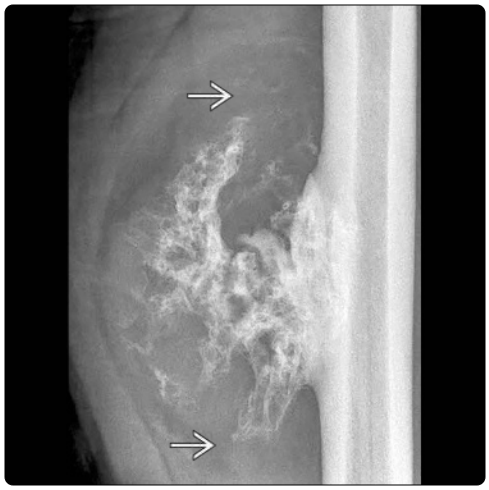


### MR of Lipoma of Bone

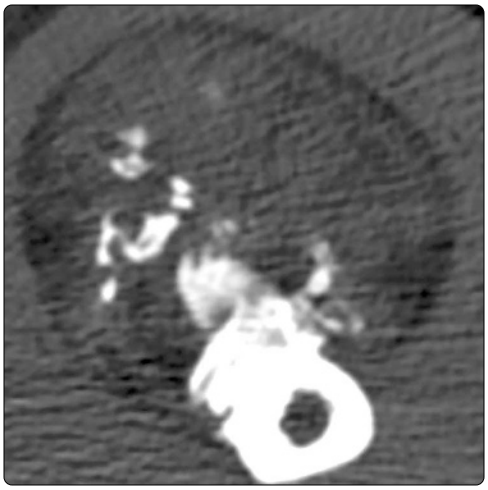


**(Left)** *This graphic shows a cut section of a femur containing an intraosseous lipoma. The lipoma appears somewhat lobulated without necrosis or calcifications.* **(Right)** *In this sagittal T1-weighted MR, an intraosseous ossifying lipoma occupies the humeral head and neck. The lipoma is well circumscribed being surrounded by a thin rim of dark bone and has high signal intensity. In the center of the tumor there is mineralized bone.*

### Parosteal Lipoma

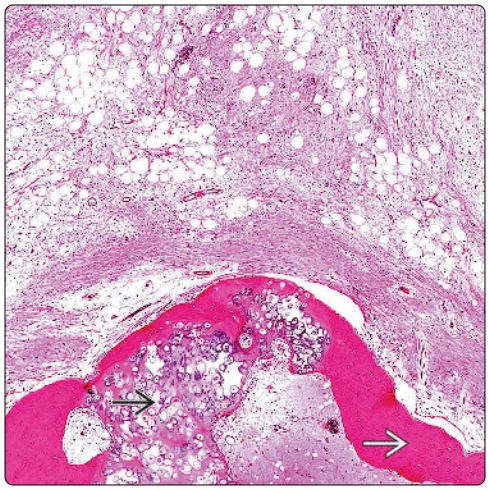


### Axial CT of Parosteal Lipoma

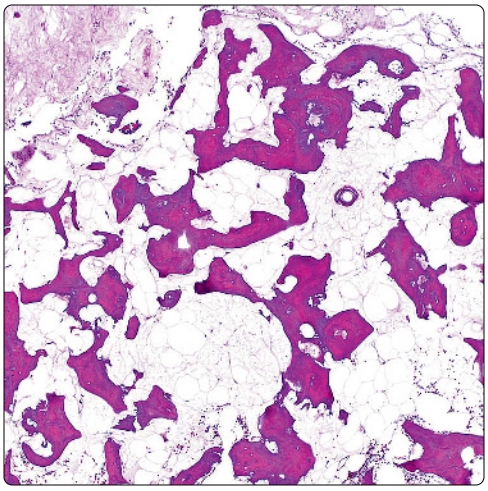


**(Left)** *A large parosteal lipoma is anchored to the underlying femoral cortex. The mass has a mineralized component most prominent at the base and extends into the body of the tumor. The mineralized element consist of calcified bone and cartilage. The fat component has low signal.* **(Right)** *On this axial CT of parosteal lipoma, the well-circumscribed tumor is shown to be attached to the underlying cortex. The mineralized matrix is scattered throughout the tumor and is most abundant at the site of anchorage.*

### Base of Parosteal Lipoma

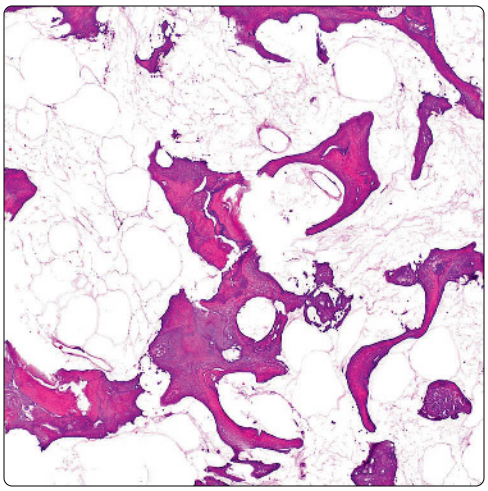


### Ossifying Lipoma

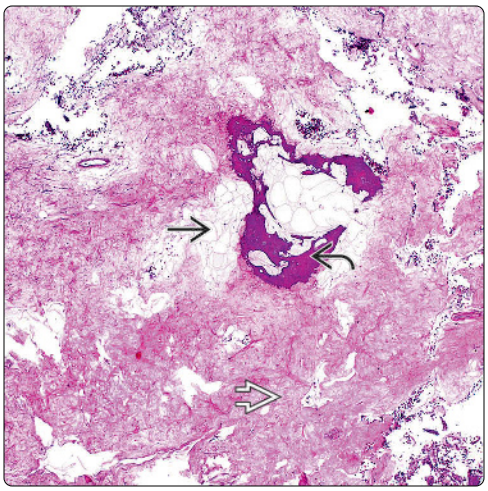


**(Left)** *Parosteal lipoma is composed of white adipocytes and varying amounts of fibrous tissue. The matrix in this case consists of mineralized cartilage and trabecular bone; it is usually most prominent at the base of the tumor.* **(Right)** *Low power shows an intraosseous lipoma that is composed of mature adipocytes, similar to conventional soft tissue lipoma, in addition to prominent irregular trabeculae of purple-pink bone. Areas like this can be easily misdiagnosed as fatty marrow.*

### Intraosseous Ossifying Lipoma

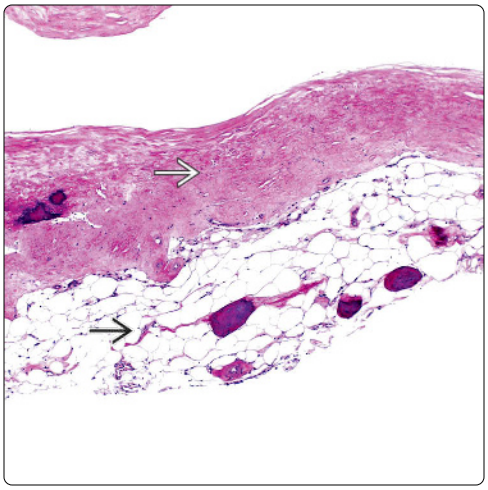


### Lipoma With Fibrosis and Bone

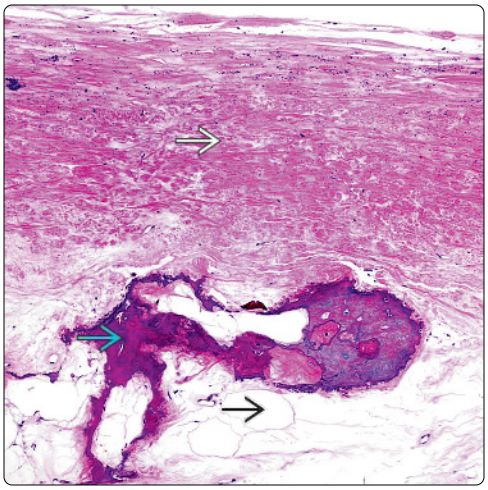


**(Left)** *This intraosseous lipoma is composed of mature adipocytes, similar to conventional soft tissue lipoma, admixed with irregular purple-pink trabeculae of woven bone.* **(Right)** *This curettage specimen from an intraosseous lipoma of the calcaneus demonstrates small islands of mature fat, extensive pink fibrosis, and focal curvilinear woven bone formation. These features are similar to what is seen in bone infarct.*

### Cystic Intraosseous Lipoma

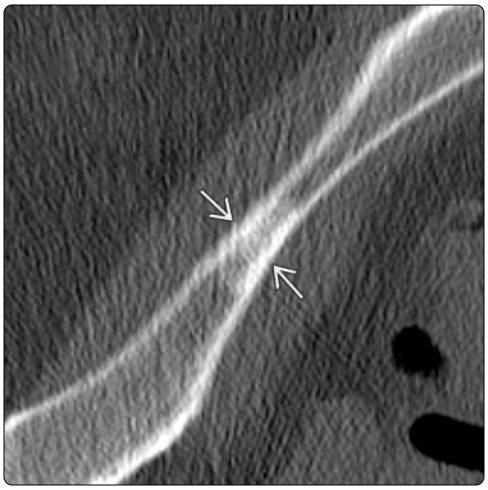


### Cystic Intraosseous Lipoma

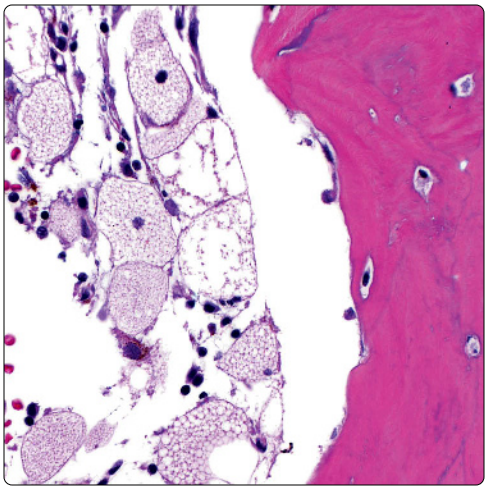


**(Left)** *This cystic intraosseous lipoma is composed of mature adipocytes, similar to conventional soft tissue lipoma, and scattered irregular, purple-colored bone formation. It has undergone cystic changes with the cystic cavity being lined by pink fibrosis.* **(Right)** *Higher power view shows a cystic intraosseous lipoma. The lipoma is composed of mature fat with woven bone trabeculae. The linking of the cyst wall is composed of pink fibrous tissue and shows some woven bone formation.*

### CT Scan of Hibernoma of Bone



### Hibernoma of Bone



**(Left)** *Axial CT scan of a hibernoma of bone is shown. The patient has a history of breast cancer and was found to have a small sclerotic lesion in the ilium. The biopsy showed an aggregated of brown fat cells.* **(Right)** *This patient presented with a sclerotic lesion of the bone. A biopsy showed a small collection of brown fat cells with granular eosinophilic cytoplasm and central small nuclei. The adjacent bone shows reactive changes.*

# Leiomyosarcoma

KEY FACTS

## TERMINOLOGY

- Sarcoma of bone showing smooth muscle differentiation microscopically, immunohistochemically, and ultrastructurally

## CLINICAL ISSUES

- Very rare primary malignant bone tumor
- Usually affects adults in 3rd-5th decades of life
- Pain
- Enlarging mass
- Pathologic fracture
- Tends to develop in long tubular bones, especially distal femur, proximal tibia, and flat bones of pelvis
- Can also arise in craniofacial skeleton
- Pain, enlarging mass, pathologic fracture
- ~ 1/2 of patients develop metastases and die from disease

## IMAGING

- Nonspecific lytic destructive mass
- Can have permeative margins
- Intralesional mineralization rare
- Destruction of cortex and accompanying soft tissue mass are common findings

## MICROSCOPIC

- Neoplastic cells usually spindle-shaped
  - Contain eosinophilic fibrillar cytoplasm
  - Nuclei are elongated and blunt ended (cigar-shaped)
  - Express markers indicative of myogenic differentiation

## TOP DIFFERENTIAL DIAGNOSES

- Metastatic leiomyosarcoma (LSM)
- Myofibroblastic sarcoma
- Leiomyoma

## DIAGNOSTIC CHECKLIST

- Always exclude metastatic LSM to bone before making diagnosis of primary intraosseous LSM

**Leiomyosarcoma of Femur**



*Leiomyosarcoma arising in the distal femur is shown. The sarcoma arises in the medullary cavity, is ill-defined, destroys the anterior cortex of the bone, and extends into the adjacent anterior soft tissue.*

## TERMINOLOGY

### Abbreviations

- Leiomyosarcoma (LMS)

### Definitions

- Sarcoma of bone showing smooth muscle differentiation microscopically, immunohistochemically, or ultrastructurally

## ETIOLOGY/PATHOGENESIS

### Neoplastic

- Most cases arise de novo
  - Rarely radiation induced

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Very rare primary malignant bone tumor
- Age
  - Usually affects adults in 3rd-5th decades of life
- Sex
  - No gender predilection

### Site

- Tends to develop in long tubular bones, especially distal femur, proximal tibia, and flat bones of pelvis
  - Can also arise in craniofacial skeleton

### Presentation

- Pain, enlarging mass, pathologic fracture

### Prognosis

- ~ 1/2 of patients develop metastases and die from disease

## IMAGING

### Radiographic Findings

- Lytic destructive mass
- Can have permeative margins
- Centered in medullary cavity
- Destruction of cortex and accompanying soft tissue mass are common findings
- Intralesional mineralization is rare

### MR Findings

- Hypointense on T1-weighted images
- Iso- or hypointense on T2-weighted images

### CT Findings

- Destructive lytic mass

## MACROSCOPIC

### General Features

- Firm
- Tan-white
- Areas of hemorrhage and necrosis present in high-grade neoplasms
- Infiltrative pattern of growth, replacing marrow and surrounding bony trabeculae

### Size

- Usually > 5 cm in diameter

## MICROSCOPIC

### Histologic Features

- Neoplastic cells are spindle-shaped and demonstrate pleomorphism and hyperchromasia
  - Cytoplasm is eosinophilic and fibrillar
  - Nuclei are elongate with blunt ends (cigar-shaped)
  - Fascicles of neoplastic cells intersecting at 90° angles
- Degree of cytologic atypia, mitotic activity, and necrosis correlates with grade of tumor

## ANCILLARY TESTS

### Immunohistochemistry

- Tumor cells express markers indicative of myogenic differentiation
  - Neoplastic cells are positive for muscle-specific actin, smooth muscle actin, and desmin

### Ultrastructural Features

- Thin filaments with dense bodies
- Subplasmalemmal attachment plaques
- Pinocytotic vesicles
- Basal lamina
- Round-ended nuclei often with indentations

## DIFFERENTIAL DIAGNOSIS

### Metastatic Leiomyosarcoma

- Much more common than primary LSM of bone
  - Uterus is common site of origin
- Should be excluded before diagnosis of primary LSM of bone is rendered

### Myofibroblastic Sarcoma

- Cells have amphophilic rather than eosinophilic cytoplasm
- Tapered instead of round-ended nuclei
- Immunohistochemically, tumor cells stain for some but not all muscle markers (desmin, muscle actin, smooth muscle actin) and staining is patchy
- Ultrastructural examination shows myofibroblastic differentiation
  - Cells with dilated rough endoplasmic reticulum and peripheral filaments with densities

### Leiomyoma

- Leiomyoma of bone is exceedingly rare
- Similar to soft tissue leiomyoma in that there is no cytologic atypia or mitotic activity

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Always exclude metastatic LSM to bone before making diagnosis of primary intraosseous LSM

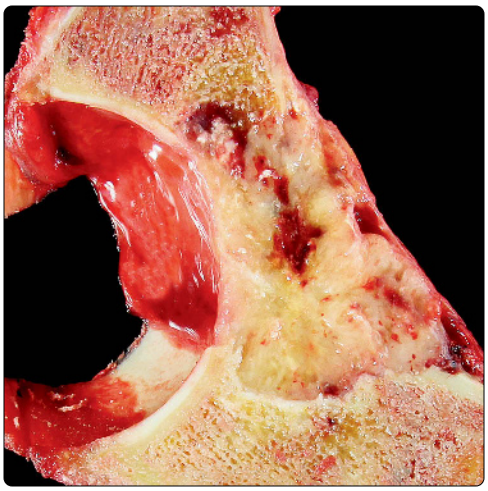
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**Destructive Leiomyosarcoma**



**Fish Flesh-Like Appearance**

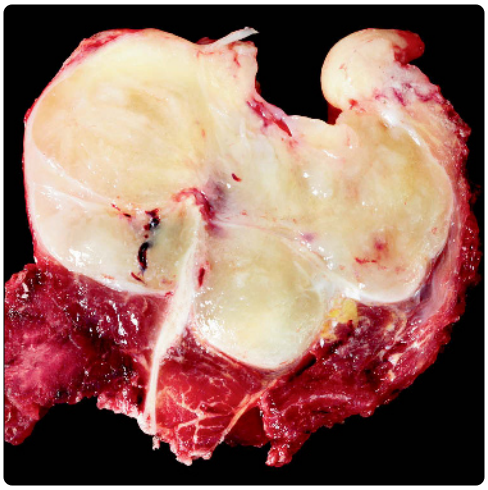


**(Left)** *Leiomyosarcoma of the medial acetabulum shows a geographic lytic lesion with no internal matrix. Medially, there is a linear ossific density from a partially destroyed ilioischial line. No soft tissue extension is seen.* **(Right)** *Leiomyosarcoma of bone involving the periacetabular area shows a tan-yellow tumor with focal areas of hemorrhage. The tumor destroys the cortex and extends into adjacent soft tissues.*

**MR of Metastatic Leiomyosarcoma**

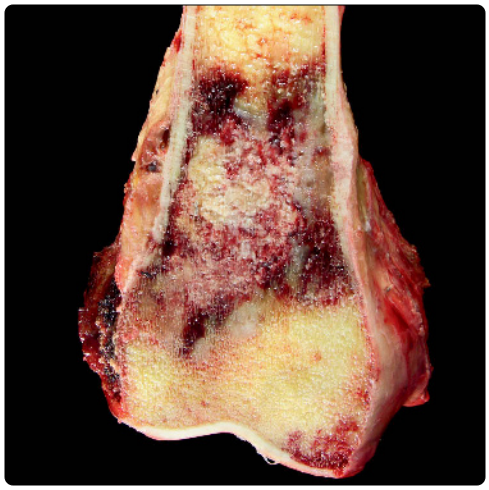


**Metastatic Leiomyosarcoma to Bone**

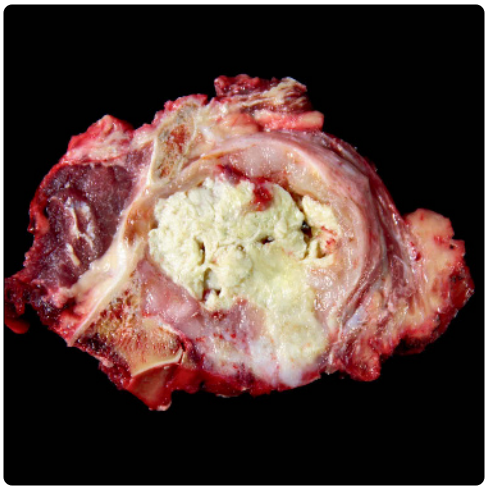


**(Left)** *This patient had a history of a leiomyosarcoma of the uterus. This metastasis of the pelvis is centered in the bone, has destroyed the cortex, and formed large intrapelvic ⇨ and extrapelvic ⇨ soft tissue extensions.* **(Right)** *Corresponding gross of a metastatic high-grade leiomyosarcoma to the pelvis is shown. The sarcoma has a fleshy appearance, has destroyed the bone, and formed a large soft tissue component. The patient had a history of a leiomyosarcoma of the uterus.*

**Poorly Defined Mass**

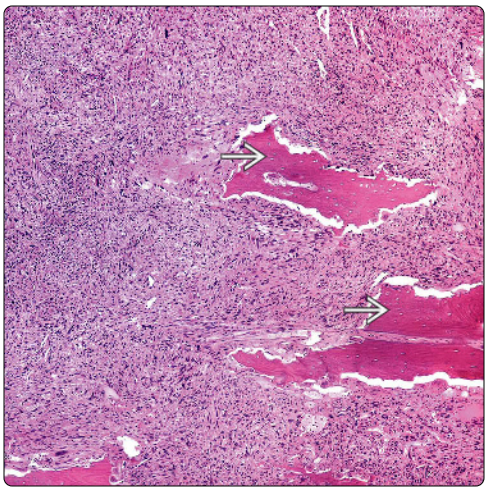


**Leiomyosarcoma of Ilium**

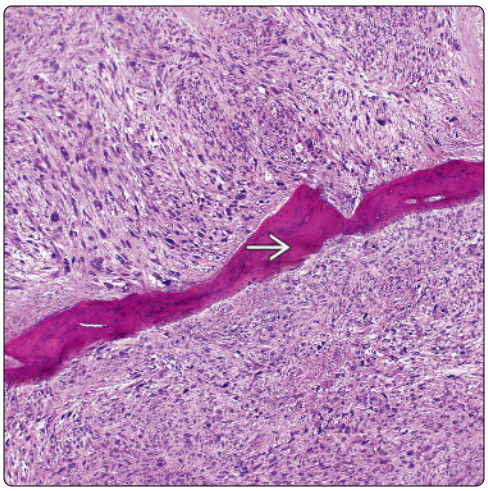


**(Left)** *Resected leiomyosarcoma of the distal femur is shown. The tumor involves the diaphysis of the bone and extends into the metaphysis. The tumor is fleshy with areas of hemorrhage and necrosis. It has destroyed the cortex and focally extended into the soft tissues.* **(Right)** *Leiomyosarcoma arising in the pelvis is shown. The tumor is tan-red and fleshy with a large central yellow-white area of necrosis. The tumor has destroyed the bone and extended into adjacent soft tissues.*

### Infiltrative Growth Pattern

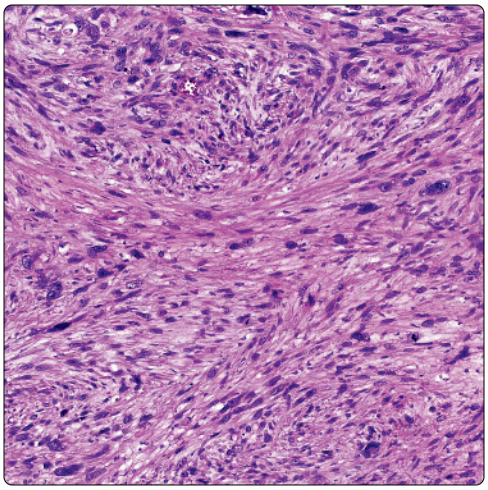


### Tumor Encasing Bone

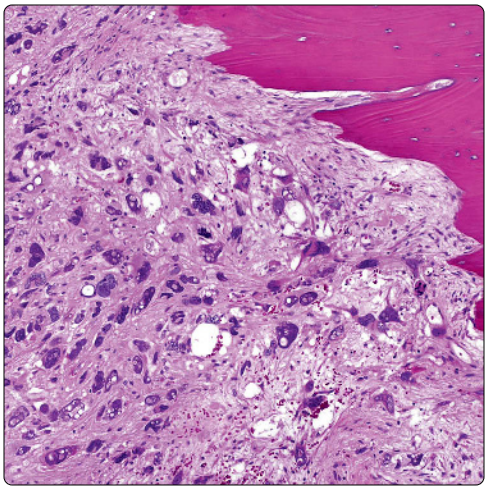


**(Left)** *High-grade leiomyosarcoma of bone is shown. The tumor is cellular and atypical and demonstrates an infiltrative growth pattern with encasement of preexisting trabecular bone* ⇒. **(Right)** *Leiomyosarcoma of bone grows with an infiltrative growth pattern. The tumor has replaced the marrow spaces and encases a preexisting trabecula of bone* ⇒.

### Pleomorphic Spindle Cells

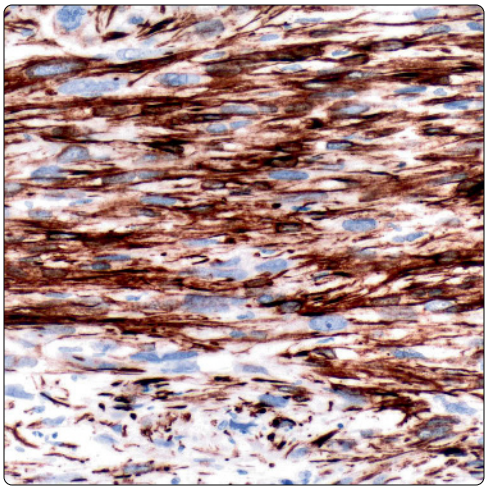


### Pleomorphic Leiomyosarcoma

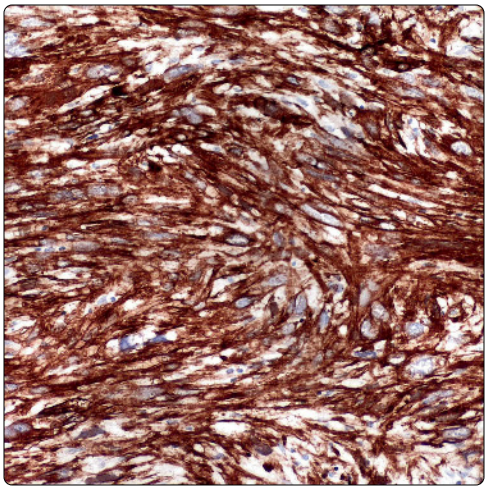


**(Left)** *The neoplastic cells in leiomyosarcoma of bone have a fascicular and vague storiform growth pattern. The cells are spindle-shaped with elongate nuclei and eosinophilic fibrillar cytoplasm.* **(Right)** *High-grade pleomorphic leiomyosarcoma of bone . The neoplastic cells demonstrate high-grade nuclear atypia and mitotic activity mimicking a high-grade pleomorphic sarcoma. Immunohistochemical studies confirmed the diagnosis of a leiomyosarcoma.*

### Desmin



### Smooth Muscle Actin



**(Left)** *In this leiomyosarcoma of bone, there is diffuse and strong expression of desmin.* **(Right)** *Leiomyosarcoma of bone shows diffuse cytoplasmic staining for smooth muscle actin. In this case, the positive staining for desmin smooth muscle actin supports the diagnosis of a leiomyosarcoma.*

# Myoepithelioma

KEY FACTS

## TERMINOLOGY

- Neoplasm showing myoepithelial differentiation

## CLINICAL ISSUES

- Myoepithelioma of bone is very uncommon
- Most frequently affects head and neck area, followed by ilium, then tibia
- Presenting symptom is usually pain of variable duration

## IMAGING

- Radiolucent, well circumscribed with sclerotic margins
- Tumor can erode cortex but remains confined by periosteum
- Malignant tumors show aggressive radiographic features

## MICROSCOPIC

- Benign myoepithelioma is well circumscribed and does not demonstrate infiltrative growth pattern
- Neoplastic cells show solid, lobulated, reticular, or storiform growth pattern
- Cells are spindle-shaped, epithelioid, or round with eosinophilic or clear cytoplasm
- Malignant myoepithelioma shows increased cellularity, atypia, mitoses, and infiltrative growth pattern

## ANCILLARY TESTS

- Immunohistochemistry shows expression of vimentin and S100 and variable expression for EMA and SMA
- FISH has shown that many intraosseous tumors, like their soft tissue counterparts, have *EWSR1* rearrangement

## TOP DIFFERENTIAL DIAGNOSES

- Desmoplastic fibroma
- Myxoid chondrosarcoma
- Chondromyxoid fibroma
- Extraskeletal myxoid chondrosarcoma
- Chordoma
- Sarcomatoid carcinoma

**Destructive Mass**



*This malignant myoepithelioma arising in the distal tibia is gray and fleshy with areas of cystic changes and hemorrhage. It has destroyed the cortex and is covered by a thin layer of periosteum.*

**Lytic Tumor With Periosteal Reaction**



*Pathologic fracture through a lytic lesion in the distal tibia (in cast) with fairly well-defined margins is shown. There is cortical penetration both medially and laterally.*

## TERMINOLOGY

### Definitions

- Neoplasm showing myoepithelial differentiation
  - Based on histologic appearance of neoplastic cells in conjunction with immunohistochemical profile
  - Historically, some myoepitheliomas have been called parachordoma

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Myoepithelioma of bone is very uncommon
- Age
  - Young to middle-aged individuals
  - Age range: 14-55 years
- Sex
  - M = F

### Site

- Most common location
  - Head and neck
    - Especially maxilla
- Outside craniofacial area ilium is most frequently affected
  - Followed by tibia and other long bones
- Usually intraosseous
  - Can also arise on surface of bone
    - Juxtacortical myoepithelioma

### Presentation

- Usually painful
  - Symptoms are variable

### Treatment

- Curettage or simple excision seems to be adequate treatment for benign tumors
- Malignant tumors need to be treated with radical surgery and possible systemic therapy

### Prognosis

- Most myoepitheliomas of bone have behaved in benign fashion
  - Recurrence is uncommon
- Rarely can be malignant and metastasize

## IMAGING

### Radiographic Findings

- Radiolucent
- Well circumscribed
  - Margins are frequently sclerotic
- Can erode cortex but remains confined by periosteum
- Periosteal new bone formation may be present
- Malignant tumors show aggressive radiographic features with bone destruction and soft tissue mass

### MR Findings

- Hypointense on T1
- Heterogeneous signal intensity on T2-weighted images
- Helpful in determining extent of tumor involvement

### CT Findings

- Homogeneous in density
- Unilocular
- Well-defined margins
- Helpful in determining extent of tumor involvement

## MACROSCOPIC

### General Features

- Mucoid or cartilaginous-like in appearance
  - Usually arises in medullary cavity or on surface of bone
- Red, gray, or pink focally hemorrhagic cut surface
- Malignant tumor features
  - Poorly defined
  - Tan
  - Hemorrhagic
  - Extend into soft tissues

## MICROSCOPIC

### Histologic Features

- Benign myoepithelioma of bone is well circumscribed
- Does not demonstrate infiltrative growth pattern
- Neoplastic cells show solid, lobulated, reticular, or storiform growth pattern
- Cells are spindle-shaped, epithelioid, or round with eosinophilic or clear cytoplasm
- No necrosis or cytologic atypia
  - Rare mitotic figures
- Extracellular matrix is collagenous, hyalinized, or myxoid
- Malignant myoepithelioma exhibits aggressive histological features
  - Increased cellularity
  - Atypia
  - Mitoses
  - Infiltrative growth pattern

## ANCILLARY TESTS

### Immunohistochemistry

- Vast majority express vimentin and S100 protein
  - Some tumors are EMA and SMA (+)
  - Sometimes, tumor cells may not express
    - Keratin
    - CD34
    - p63
    - Desmin
    - GFAP

### Genetic Testing

- FISH has shown that many intraosseous tumors, like their soft tissue counterparts, have *EWSR1* gene rearrangement
- *EWSR1* translocation partners are variable; they include
  - *POU5F1*
  - *PBX1*
  - *ZNF444*
  - *ATF1*
  - *PBX3*
  - *KLF17*
- Other translocations have rarely been identified
  - *FUS-KLF17* rarely present

## DIFFERENTIAL DIAGNOSIS

### Desmoplastic Fibroma

- Composed of fascicles of spindle-shaped cells embedded in collagenous matrix
  - Similar histologic appearance as soft tissue fibromatosis
- Neoplastic cells do not stain for S100 protein or epithelial markers
- Lack chromosomal abnormalities involving chromosome 22

### Myxoid Chondrosarcoma

- Composed of round to stellate neoplastic cells
  - Cord-like growth pattern
  - Abundant extracellular myxoid matrix
- Myxoid chondrosarcomas are S100(+)
  - They usually do not stain for epithelial markers
  - Do not demonstrate *EWSR1* rearrangement

### Chondromyxoid Fibroma

- Displays lobulated growth pattern
  - Lobules have hypocellular center with increased cellularity toward periphery
- Cells are stellate or spindle-shaped
  - Embedded in abundant extracellular myxoid matrix
- They can express S100 protein
  - They do not stain for epithelial markers
  - Lack chromosome 22 translocations

### Extraskeletal Myxoid Chondrosarcoma

- Most extraskeletal myxoid chondrosarcomas arise in soft tissue
- Rare cases can arise in bone
- Histologically, neoplastic cells have nested and reticular growth pattern and are embedded in abundant extracellular myxoid stroma
  - Which histologically can be difficult to distinguish from myoepithelial tumors
- Can express S100 and epithelial membrane antigen
  - Usually keratin (-)
- Genetically have *EWSR1* gene rearrangement like myoepithelioma
  - Other rearrangements include involvement of following: *TFG, TCF12, TAF15*
  - All of these genes show translocation involving *NR4A3* on chromosome 9, which is not present in myoepithelioma
    - FISH for *NR4A3* is very helpful in distinguishing extraskeletal myxoid chondrosarcoma from myoepithelioma

### Chordoma

- Usually arises in axial skeleton
  - Can rarely arise in extraaxial location
- Histologically can mimic myoepithelioma
- Chordoma express S100 and epithelial markers similar to myoepithelioma
  - Chordoma also expresses brachyury
    - Very specific and sensitive marker for chordoma
      - Myoepithelioma is negative for brachyury

### Sarcomatoid Carcinoma

- Might enter into differential diagnosis due to expression of epithelial markers
- Sarcomatoid carcinoma shows more cytologic atypia than myoepithelioma of bone

## DIAGNOSTIC CHECKLIST

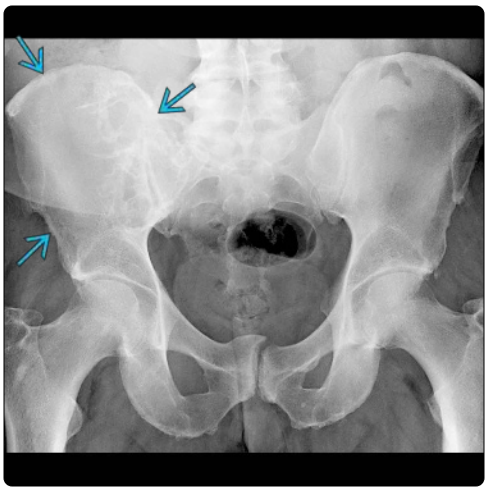
### Pathologic Interpretation Pearls

- Myoepithelioma of bone is rare and should be considered in differential diagnosis of unusual tumor that expresses epithelial markers

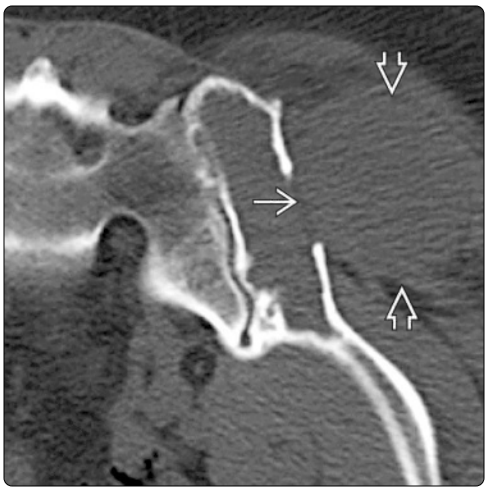
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### Myoepithelioma of Pelvis



### CT of Myoepithelioma of Ilium

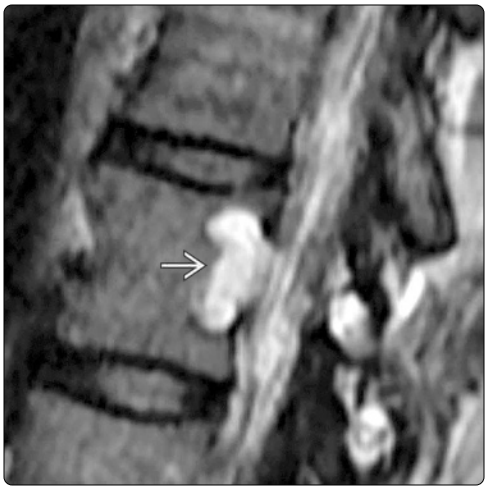


**(Left)** *A radiograph of the pelvis demonstrates a mixed lytic and sclerotic lesion involving the right ilium with sclerotic margins and internal septations.* **(Right)** *Axial CT scan of a histologically benign intraosseous myoepithelioma of the ilium shows marrow replacement by the tumor that has soft tissue density. There is cortical disruption with a large, rounded soft tissue mass extending out into the adjacent soft tissues.*

### T1 MR of Pelvic Myoepithelioma



### Vertebral Myoepithelioma



**(Left)** *Coronal T1-weighted MR with fat saturation following intravenous gadolinium shows an enhancing myoepithelioma within the posterior Ilium extending into soft tissues. Note the adjacent edema and inflammation of the soft tissues.* **(Right)** *Sagittal T2-weighted MR of another histologically benign myoepithelioma of the bone shows a hyperintense lesion in the posterior body and posterior elements of the vertebra with an epidural component.*

### Myoepithelioma of Tibia

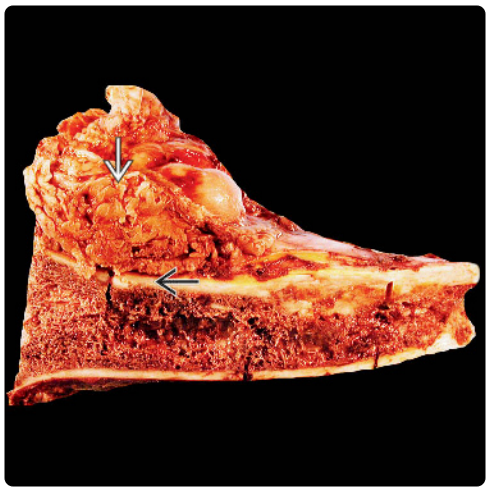


### Myoepithelioma of Tibia

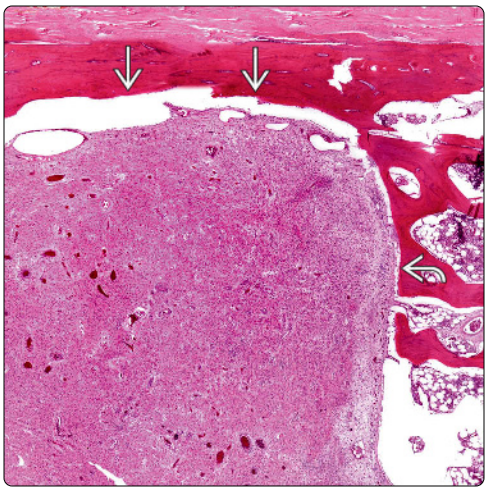


**(Left)** *Myoepithelioma arising in the mid shaft of the tibia is shown. The mass is mixed lytic and radiodense and has fairly well-circumscribed margins.* **(Right)** *Oblique radiograph of the lower leg demonstrates a well-defined lesion in the distal tibia with a thin, sclerotic rim. The radiographic features are similar to a nonossifying fibroma of bone; however, the biopsy showed a myoepithelioma that contains EWSR1 gene rearrangement.*

**Juxtacortical Myoepithelioma**

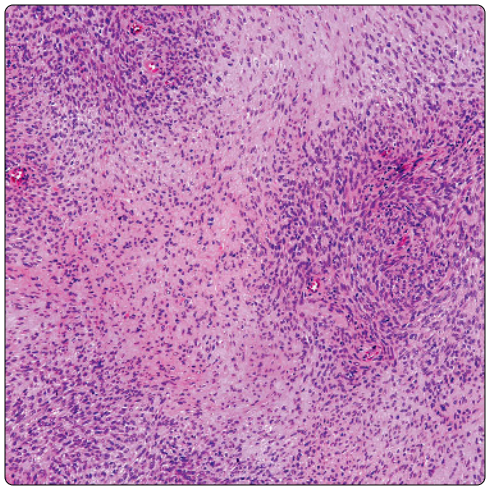


**Well-Demarcated Lesion**

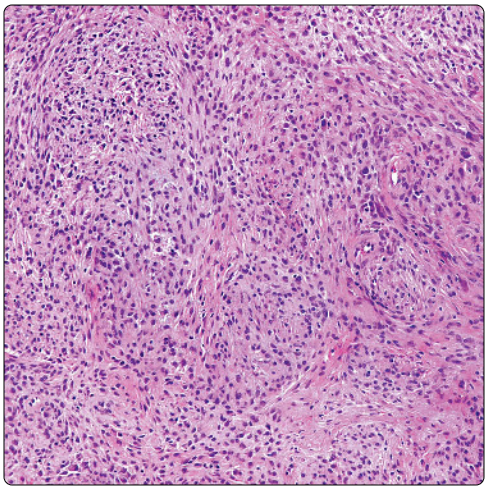


**(Left)** *This myoepithelioma arises on the surface of the long bone and displaces the periosteum. The tumor is tan-red and multilobulated. The underlying cortex is intact and the medullary cavity is not involved.* **(Right)** *Primary intraosseous myoepithelioma of bone is shown. The tumor is cellular with prominent blood vessels. It has well-defined margins within the cortical and cancellous bone and does not demonstrate an infiltrative growth pattern.*

**Spindle-Shaped Cells**

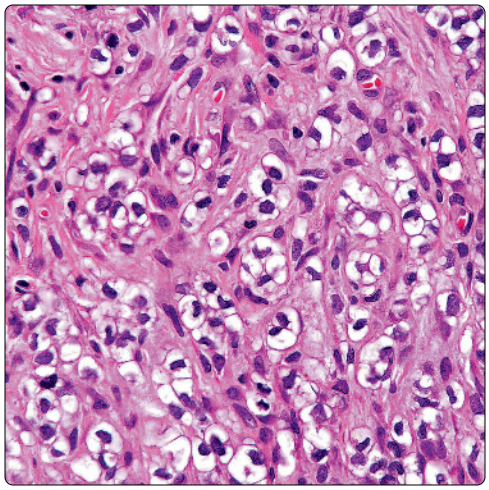


**Spindle-Shaped Cells**

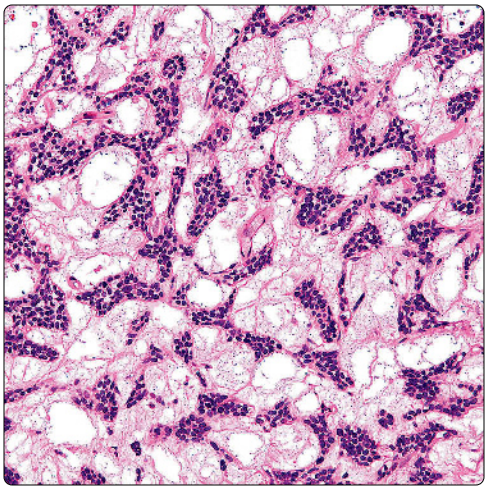


**(Left)** *This intraosseous myoepithelioma is composed of plump, spindle-shaped cells that are arranged in intersecting fascicles.* **(Right)** *Higher power view shows an intraosseous myoepithelioma that is composed of bland-looking, spindle-shaped cells with a vague fascicular growth pattern.*

**Clear Cells**

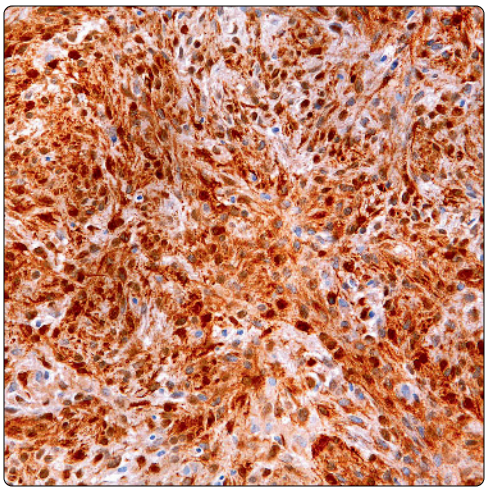


**Nests and Cords**

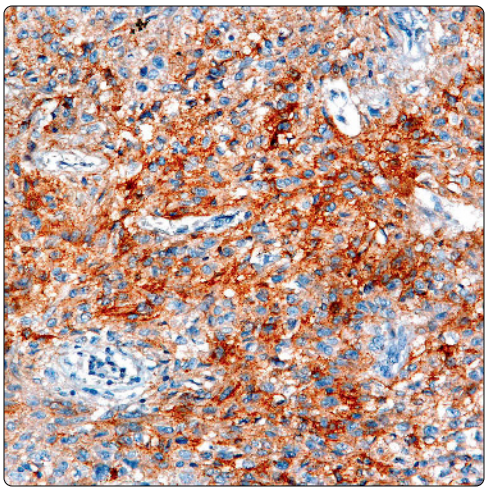


**(Left)** *This benign myoepithelioma of bone is composed of small nests and cords of cells with clear cytoplasm, separated by a pink collagenous stroma. There is minimal nuclear pleomorphism and no mitotic activity.* **(Right)** *This unusual myoepithelioma of bone, which arose in the vertebra, has a corded, nested, and somewhat reticulated growth pattern. The cells are small with small nuclei and eosinophilic cytoplasm. The stroma is myxoid with some collagen fibers.*

S100

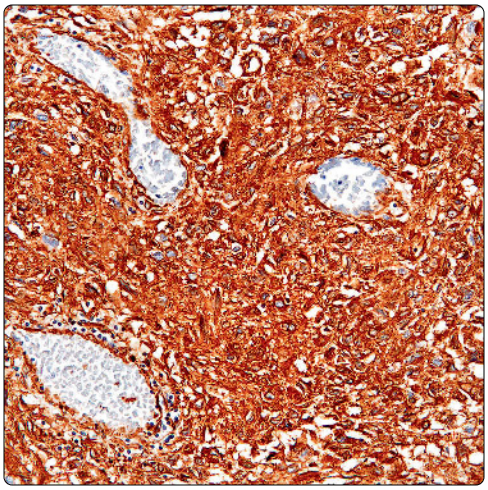


Epithelial Membrane Antigen

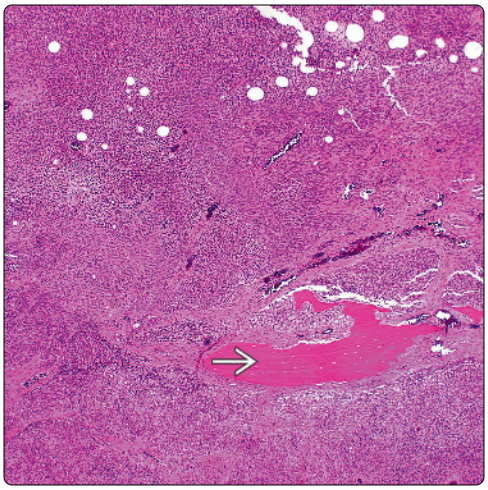


**(Left)** *Intraosseous myoepithelioma with diffuse and strong cytoplasmic and nuclear staining for S100 is shown.* **(Right)** *Intraosseous myoepithelioma stained for epithelial membrane antigen shows that numerous cells demonstrate membranous and cytoplasmic staining for this antibody.*

Smooth Muscle Actin

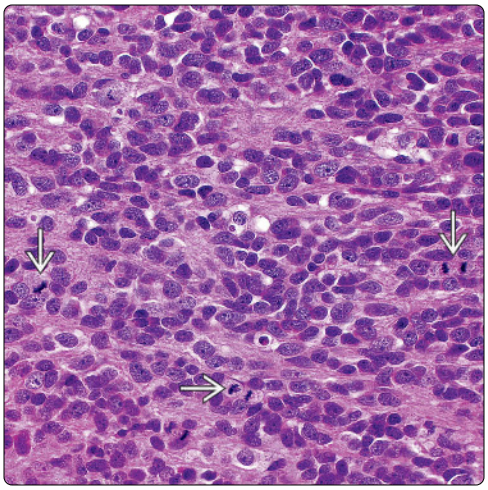


Malignant Myoepithelioma

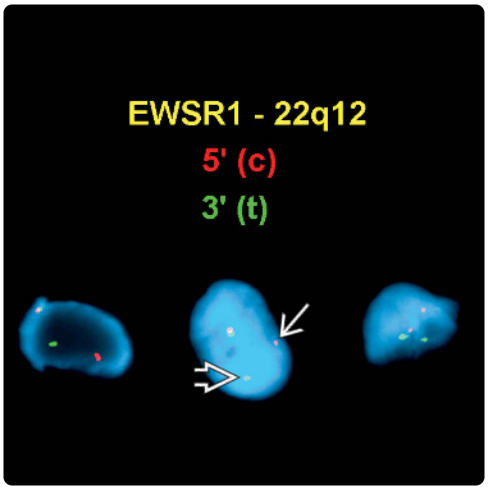


**(Left)** *Intraosseous myoepithelioma shows strong, diffuse cytoplasmic staining for smooth muscle actin.* **(Right)** *This malignant myoepithelioma demonstrates the histologic features of a malignant neoplasm. The tumor is cellular and grows with an infiltrative growth pattern encasing preexisting trabecular bone ➔. The tumor stained for epithelial membrane antigen and showed EWSR1 rearrangement confirming the diagnosis.*

Malignant Myoepithelioma



FISH for *EWSR1*




**(Left)** *This high-power view of a malignant myoepithelioma demonstrates a cellular neoplasm with cytologic atypia and numerous mitotic figures ➔. The tumor arose in the tibia and had an infiltrative growth pattern.* **(Right)** *Fluorescent in situ hybridization using a break-apart probe shows rearrangement of the EWSR1 gene on chromosome 22q12, demonstrated by the separation of the red ➔ and green ➔ signals supporting the diagnosis of a myoepithelioma.*

# Schwannoma

KEY FACTS

## TERMINOLOGY

- Benign bone tumor composed of Schwann cells

## ETIOLOGY/PATHOGENESIS

- Most tumors are sporadic; rarely seen in Carney complex and schwannomatosis
  - Arise from intraosseous nerves

## CLINICAL ISSUES

- Rare primary benign bone tumor
- Sites affected: Jaw, petrous apex, sacrum, long bones
- Pain is common presenting symptom
- Removal by curettage or enucleation
- Local recurrence uncommon

## IMAGING

- Radiolucent and expansile
- Heterogenous on T1- and T2-weighted images
- Minority cystic with fluid levels
- Rarely, soft tissue extension present

## MACROSCOPIC

- 1.5-9.0 cm; sacral tumors often large

## MICROSCOPIC

- Features of conventional schwannoma with Antoni A and B regions and Verocay bodies
- Melanotic schwannoma very rare
- Ancient change may be present; limited mitotic activity

## ANCILLARY TESTS

- Diffusely and strongly positive for S100 protein and SOX10

## TOP DIFFERENTIAL DIAGNOSES

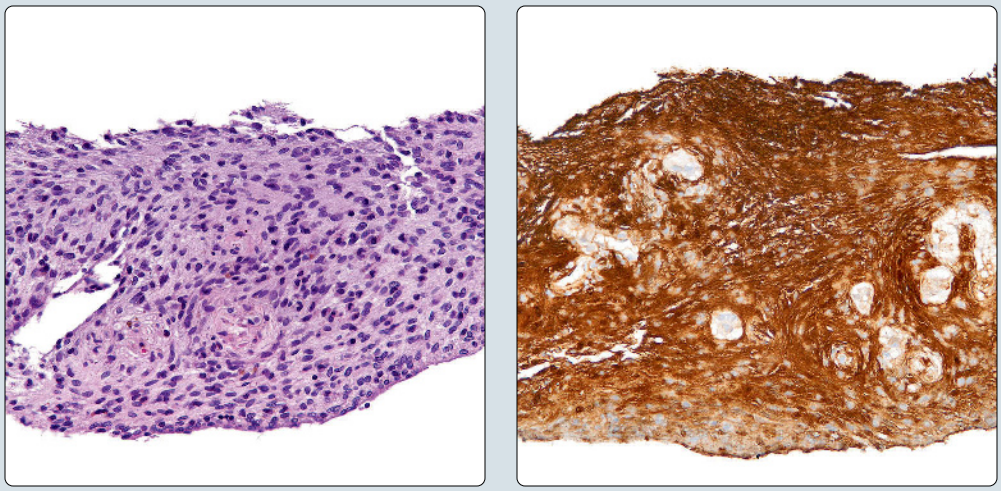
- Metastatic melanoma
- Malignant peripheral nerve sheath tumor

**Large Sacral Schwannoma** | **Multilobated Schwannoma**



**(Left)** *The sacrum distal to S1 is expanded by a large, lytic, mass whose proximal margin is well circumscribed and sclerotic. Within the mass are some linear trabeculations.* **(Right)** *Axial T1-weighted MR shows that the sacrum is expanded by a solid mass. The tumor is well circumscribed and has a prominent nodular configuration. The tumor does not invade the neighboring soft tissues.*

**Needle Biopsy of Schwannoma** | **S100 Staining**



**(Left)** *Needle biopsy of an intraosseous schwannoma shows a moderately cellular neoplasm composed of bland-appearing, oval to spindle-shaped cells that are arranged in short fascicles. Some of the tumor cells are comma-shaped.* **(Right)** *Intraosseous schwannoma is composed of spindle cells that raise the differential diagnosis of a variety of tumors. Immunohistochemistry is important in the evaluation, and the strong staining for S100 protein is helpful in confirming the diagnosis of schwannoma.*

## TERMINOLOGY

### Synonyms

- Neurilemmoma

### Definitions

- Benign bone tumor composed of Schwann cells

## ETIOLOGY/PATHOGENESIS

### Neoplasm

- Most tumors are sporadic
- Rarely reported in Carney complex and schwannomatosis

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Rare primary benign bone tumor
    - Accounts for < 0.2% of all primary bone tumors
- Age
  - Usually affects adults; mean age: 35 years
    - Can occur in all age groups
- Sex
  - Slightly more common in females

### Site

- Jaw, petrous apex, sacrum, vertebrae, long bones
  - Arise from nerves in medullary cavity some adjacent to nutrient artery

### Presentation

- Pain
- Radiculopathy for spinal tumor
- Incidental finding discovered on imaging studies

### Treatment

- Removal by curettage or enucleation

### Prognosis

- Local recurrence uncommon

## IMAGING

### Radiographic Findings

- Oval or round
- Radiolucent
- Expansile
- Well-defined sclerotic margins
- Rarely, soft tissue extension present

### MR Findings

- Heterogenous on T1- and T2-weighted images
  - Minority cystic with fluid levels
- No surrounding edema

### CT Findings

- Lesion similar or hypodense to muscle

### Bone Scan

- May show increased uptake on bone scan

## MACROSCOPIC

### General Features

- Well circumscribed
- Soft
- Tan-yellow with areas of hemorrhage

### Size

- 1.5-9.0 cm; sacral tumors often large

## MICROSCOPIC

### Histologic Features

- Features characteristic of conventional schwannoma with Antoni A and B regions and Verocay bodies
  - Some are cellular and composed of Antoni A regions
  - Ancient change may be present; limited mitotic activity
  - Rarely plexiform
- Rarely melanin pigment present
  - Psammomatoid calcifications (psammomatoid melanotic schwannoma)
    - Arise in patients with Carney complex

## ANCILLARY TESTS

### Immunohistochemistry

- Diffusely and strongly positive for S100 protein and SOX10
- Melanotic schwannomas positive for melanocytic markers

## DIFFERENTIAL DIAGNOSIS

### Metastatic Melanoma

- Important to differentiate from melanotic schwannoma
  - Both have melanin pigment and can stain with melanoma markers
- Melanotic schwannoma does not demonstrate cytologic atypia seen in metastatic melanoma

### Malignant Peripheral Nerve Sheath Tumor

- Differential diagnosis especially with cellular schwannoma
- Shows more cytologic atypia, has herringbone pattern, and infiltrative growth
- Malignant peripheral nerve sheath tumor negative or focally positive for S100

### Fibrous Dysplasia, Nonossifying Fibroma, Aneurysmal Bone Cyst, Chondromyxoid Fibroma

- These are tumors in radiological differential diagnosis but are easy to distinguish histologically

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4. de la Monte SM et al: Intraosseous schwannoma: histologic features, ultrastructure, and review of the literature. Hum Pathol. 15(6):551-8, 1984
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**Schwannoma of Sacrum**

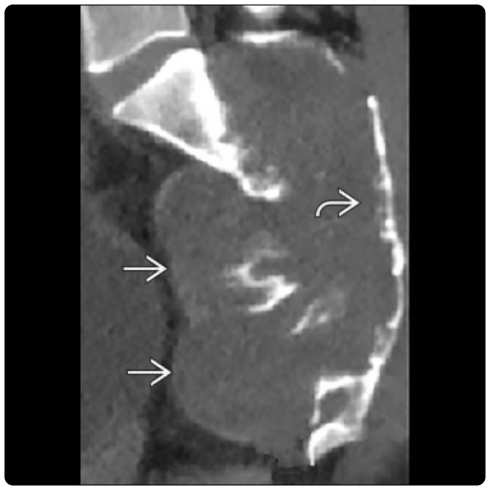


**Elongate Lytic Mass**

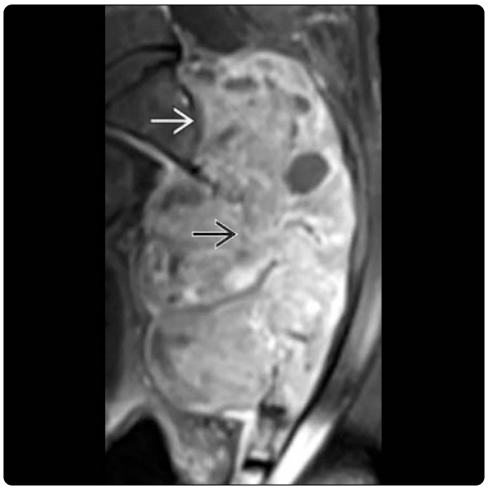


**(Left)** *Tumors of the sacrum can present with subtle findings. In this case, the tumor appears as an oblong lytic mass ⇨ that has sclerotic margins ⇨.* **(Right)** *The sacrum is distorted by an elongate lytic mass that expands the bone ➡. The anterior and posterior margins are well circumscribed and sclerotic ➡.*

**Large Schwannoma**



**MR of Schwannoma**

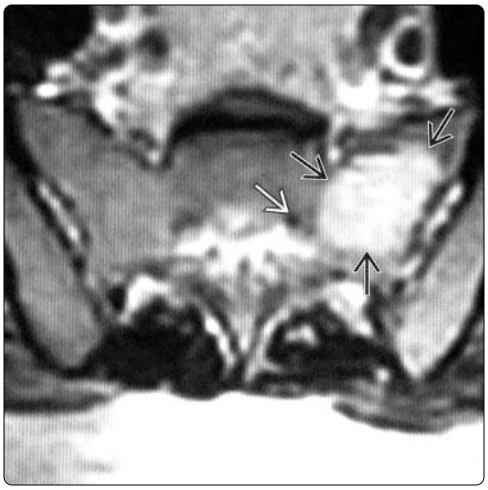


**(Left)** *A large schwannoma of the sacrum has destroyed much of the involved bone. The tumor is expansile and pushes into the anterior soft tissues ➡ where the cortex has been resorbed. The newly formed posterior cortex is largely intact ➡.* **(Right)** *In this sagittal T2 fat-saturated weighted image, the schwannoma manifests as a bright lobulated mass ⇨ with scattered hypointense regions. The tumor is well demarcated ➡ from the adjacent bone and soft tissues; no peritumoral edema is present.*

**Eccentric Sacral Schwannoma**

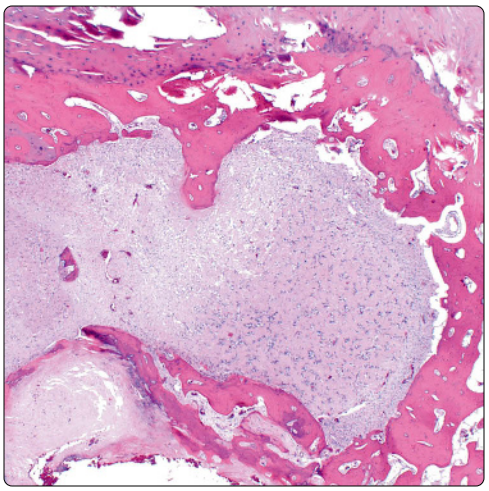


**Schwannoma in Sacral Wing**

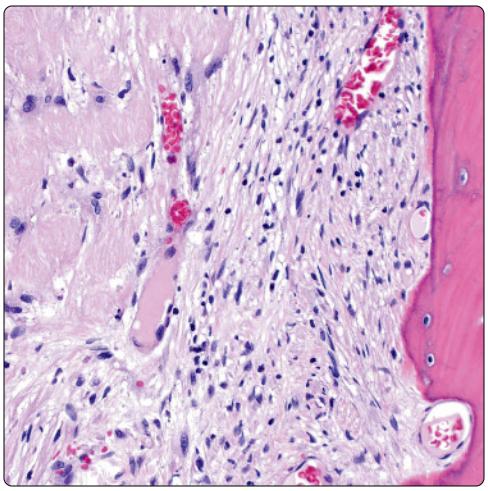


**(Left)** *This schwannoma is eccentrically located in the sacrum. The tumor has an irregular oval contour and is uniformly solid and lytic. The margins are well defined and sclerotic. A needle biopsy trocar is piercing the tumor.* **(Right)** *Axial MR of schwannoma ⇨ in the sacral that has a homogeneous bright signal is shown. The tumor is well circumscribed and adjacent to the neural foramina ➡.*

### Well-Circumscribed Margin

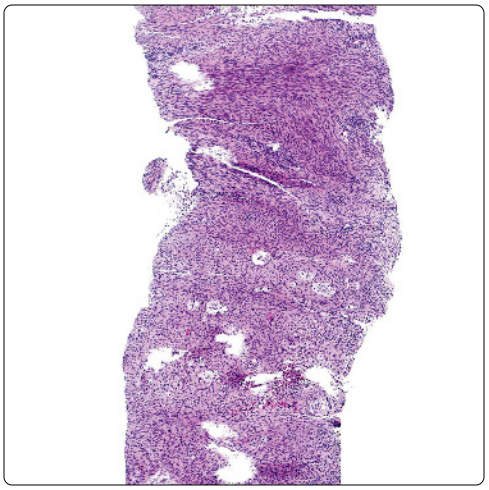


### Sharp Margin

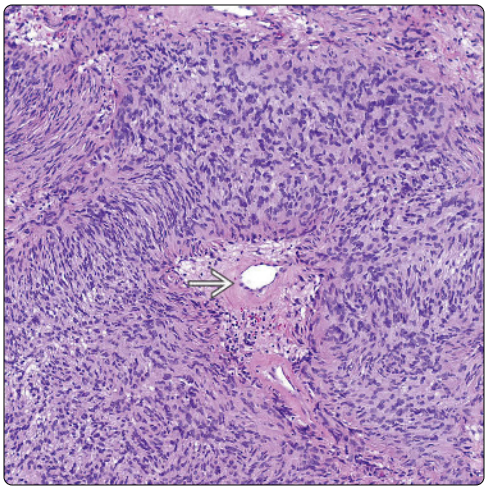


**(Left)** *Intraosseous schwannoma is slow growing and has well-circumscribed margins. The tumor is lobulated and is sharply demarcated from the adjacent bone, which is sclerotic. Notice the variation in the degree of cellularity with hypo- and hypercellular areas.* **(Right)** *Schwannoma in bone has a nodular or lobular architecture and a sharp margin with the adjacent bone. The tumor cells are spindle shaped with slight nuclear enlargement and hyperchromasia indicative of mild ancient change.*

### Needle Biopsy

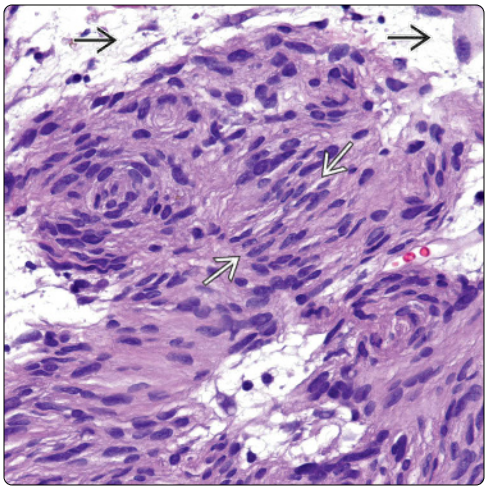


### Cellular Portion of Schwannoma

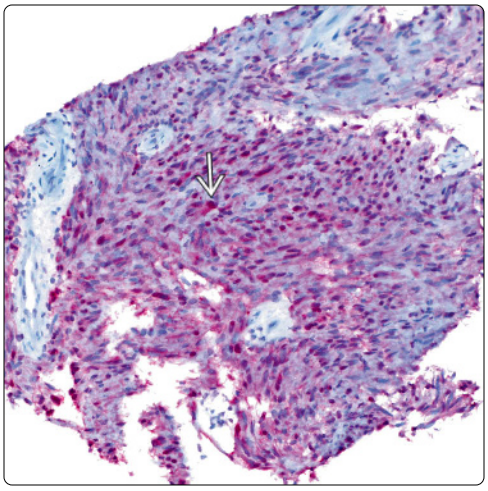


**(Left)** *Intraosseous schwannoma is often diagnosed by needle biopsy. The tumor shows the same features of schwannoma that arises elsewhere in the body. Because schwannoma can have areas of hypercellularity, as in this case, it can be confused with other forms of malignancy.* **(Right)** *The hypercellular area of schwannoma is known as Antoni A and is composed of tight bundles of spindle cells arranged in small fascicles. The intratumor blood vessels often show perivascular sclerosis ➡.*

### Antoni A Region



### Staining for S100



**(Left)** *In this schwannoma of bone, the Antoni A areas contain Verocay bodies composed of palisading spindle cells ➡. The Antoni B regions are less cellular and contain abundant myxoid stroma ⇨.* **(Right)** *Needle biopsy of intraosseous schwannoma is composed of a small fragment of spindle cells arranged in short fascicles. Immunohistochemistry can be very important in rendering the correct diagnosis; the tumor cells show strong nuclear and cytoplasmic staining for S100 protein (red chromogen) ➡.*

KEY FACTS

## CLINICAL ISSUES

- Mean age at diagnosis: 36 years (range: 6-82 years)
- M:F = 1.7:1
- Most frequent complaint is low back pain
- Nearly exclusively found in region of filum terminale
- WHO grade I tumor has excellent prognosis, particularly if resected intact
- En bloc resection is treatment of choice
- Irradiation for residual or inoperable disease

## IMAGING

- Radiolucent sacral lesion
- Well-defined margin that may be sclerotic

## MACROSCOPIC

- Tumor is surrounded by delicate fibrous capsule

## MICROSCOPIC

- Typically dominated by papillary architecture
- Papillary cores show vascular channels with hyalinization and variable amounts of myxoid matrix
- Neoplastic cells show round to oval nuclei with delicate chromatin and small solitary nucleoli

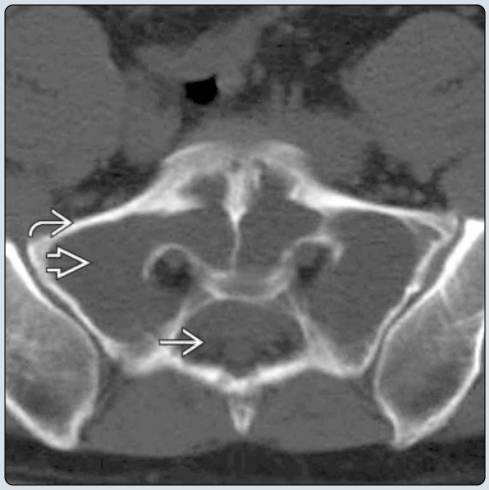
## ANCILLARY TESTS

- GFAP positive
- Keratin: May be positive

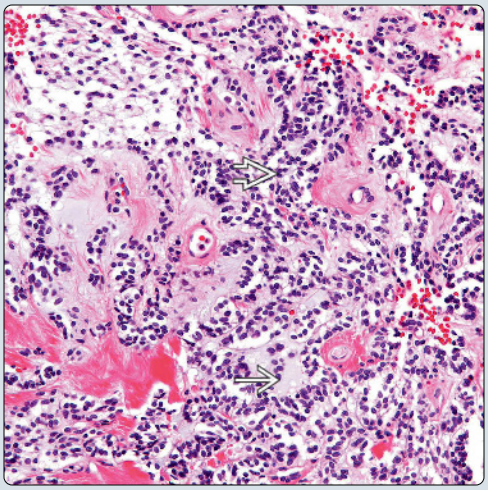
## TOP DIFFERENTIAL DIAGNOSES

- Chordoma
  - Positive for brachyury
- Paraganglioma
  - Positive for chromogranin and synaptophysin
- Metastatic adenocarcinoma
  - Typically negative for GFAP
- Schwannoma
  - Do not show papillary structures

### Myxopapillary Ependymoma

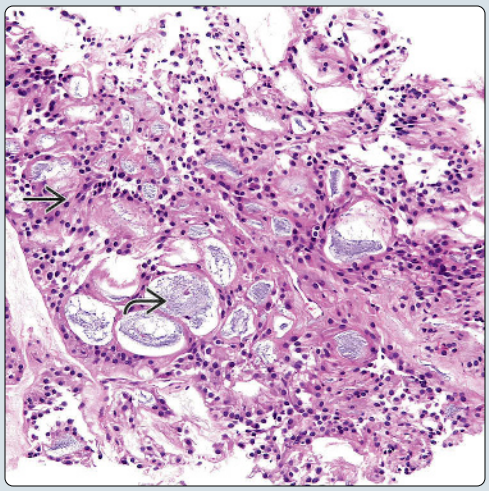


### Pseudopapillary Pattern

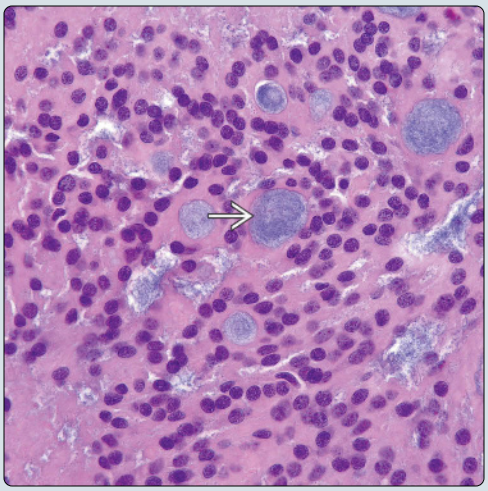


**(Left)** *Axial CT shows expansion of the spinal canal. A radiolucent lesion occupies the majority of the sacrum. Note the sclerotic perilesional bone, a findings suggesting a benign neoplasm.* **(Right)** *A myxopapillary ependymoma with prominent pseudopapillary pattern is show. The core of the pseudopapillary structures is hyalinized and shows a single central vascular channel. Note the foci with mucin accumulation. The neoplastic cells show a monotonous appearance and lack nuclear atypia.*

### Microcystic Spaces



### Epithelioid Cells



**(Left)** *Myxopapillary ependymoma shows microcystic spaces filled with mucoid material. Bipolar fibrillated ependymal cells are also seen. The tumor was diffusely positive for GFAP.* **(Right)** *The myxopapillary ependymoma shows a more solid pattern of growth with intervening mucoid cysts. The neoplasm mimics a chordoma and metastatic carcinoma because of the epithelioid cells and reactivity for keratin. Immunoreactivity for GFAP distinguishes myxopapillary ependymoma from its mimics.*

## CLINICAL ISSUES

### Epidemiology

- Age
  - Mean age at diagnosis: 36 years (range: 6-82 years)
  - 1/5 of patients are in their first 2 decades of life
- Sex
  - M:F = 1.7:1

### Site

- Nearly exclusively found in region of filum terminale
- Rare tumors occur in subcutaneous locations dorsal to sacrum and coccyx or in deep soft tissue anterior to sacrum and posterior to rectum

### Presentation

- Most frequent complaint is low back pain

### Treatment

- Surgical approaches
  - En bloc resection is treatment of choice
- Radiation
  - Irradiation for residual or inoperable disease

### Prognosis

- WHO grade I tumor with excellent prognosis, particularly if resected intact
- If capsule is breached and mucoid material spilled intraoperatively, risk of recurrence increases
- Rarely, tumor disseminates through subarachnoid space
- Subset of soft tissue examples have been reported to metastasize to lung or other organs
- Pediatric patients have more aggressive clinical course with much higher rate of local recurrence and dissemination of tumor within neural axis

## IMAGING

### Radiographic Findings

- Radiolucent sacral lesion
- Expansile
- Well-defined margins that may be sclerotic
- Erosion of vertebral bodies may be seen

## MACROSCOPIC

### General Features

- Tumor is typically surrounded by delicate fibrous capsule
- Ovoid to sausage-shaped
- Often limited to filum but may show direct proximal extension to conus medullaris or surrounding lumbosacral nerve roots
- Cut surface mucoid or hemorrhagic

## MICROSCOPIC

### Histologic Features

- Typically dominated by papillary architecture
  - Papillary cores show vascular channels with hyalinization and variable amounts of myxoid matrix
- Ependymal papillary structures are lined by cuboidal or columnar cells
- Clusters of bipolar fibrillated cells may be seen
- Neoplastic cells show round to oval nuclei with delicate chromatin and small solitary nucleoli
- Marked nuclear atypia is seen only in minority of cases
- Cytoplasmic vacuolation may be seen
  - Rare signet ring-like cells
- Tumors that are less papillary may show rounded structure referred to as balloon

### Cytologic Features

- Relatively lightly stained myxoid material with focal fibrillary appearance surrounded by elongated cells arranged around this material

## ANCILLARY TESTS

### Immunohistochemistry

- GFAP
  - Neoplastic cells are strongly positive
- Keratin: May be positive
- S100: Generally positive

### Electron Microscopy

- Long, zipper-like desmosomes and intercellular junctions
- Intraluminal or surface cilia and microvilli
- Intracytoplasmic lumina

## DIFFERENTIAL DIAGNOSIS

### Chordoma

- Primarily intraosseous neoplasm that may extend into canal
- Shows cohesive nests of epithelioid cells
- Positive for brachyury
  - Myxopapillary ependymoma is negative for brachyury

### Paraganglioma

- Lacks papillary appearance and intra- and extracellular mucin

### Metastatic Adenocarcinoma

- Presence of intra- and extracellular mucin may mimic adenocarcinoma

### Schwannoma

- Antoni A and Antoni B patterns
- Schwannomas do not show papillary patterns

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5. Anderson MS: Myxopapillary ependymomas presenting in the soft tissue over the sacrococcygeal region. Cancer. 19(4):585-90, 1966

# Phosphaturic Mesenchymal Tumor

KEY FACTS

## TERMINOLOGY

- Osteomalacia-associated mesenchymal tumor
- Distinctive mesenchymal tumor associated with oncogenic osteomalacia

## CLINICAL ISSUES

- In largest series published, 2 tumors arose in femur and 1 each in sacrum, phalanx, metacarpal, iliac crest, cervical vertebra, mandible, and tibia
- Hypophosphatemia
- Decreased 1,25-dihydroxyvitamin D3 levels

## MICROSCOPIC

- Stellate to spindle-shaped cells
- Myxoid, myxochondroid, chondroid, or osteoid matrix
- Flocculent calcified matrix often with surrounding osteoclast-type giant cells
- Prominent vasculature

## ANCILLARY TESTS

- Tumors express fibroblast growth factor 23

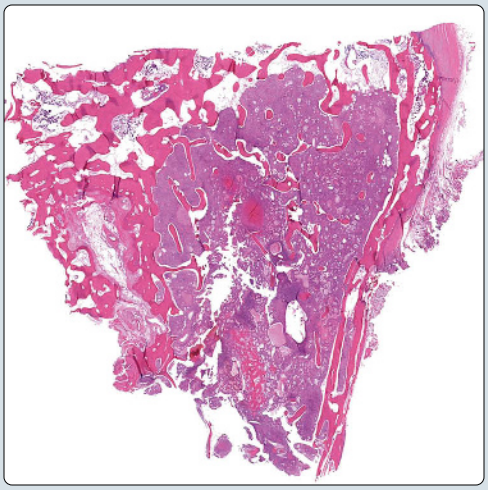
## TOP DIFFERENTIAL DIAGNOSES

- Solitary fibrous tumor
  - Patternless pattern; prominent hemangiopericytoma-like vascular pattern
  - Strongly CD34 and STAT6 positive
- Giant cell tumor of bone
  - Osteoclast-type giant cells in giant cell tumor of bone are evenly distributed, and nuclei of giant cells have nuclear features similar to mononuclear neoplastic cells
- Mesenchymal chondrosarcoma
  - Obviously malignant neoplasm
  - Composed of round and spindle-shaped cells with chondroid areas and hemangiopericytoma-like vascular pattern

**Small Lesion of Femur**

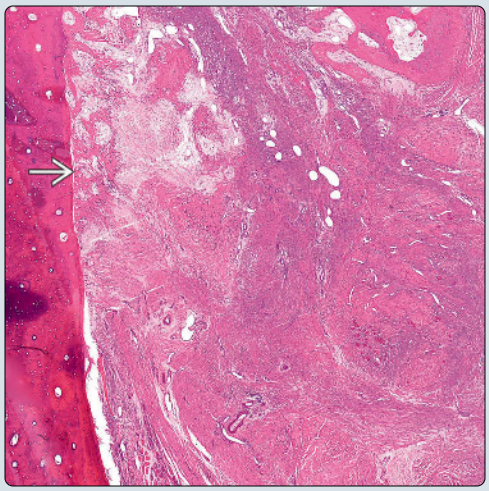


**Infiltrative Growth Pattern**

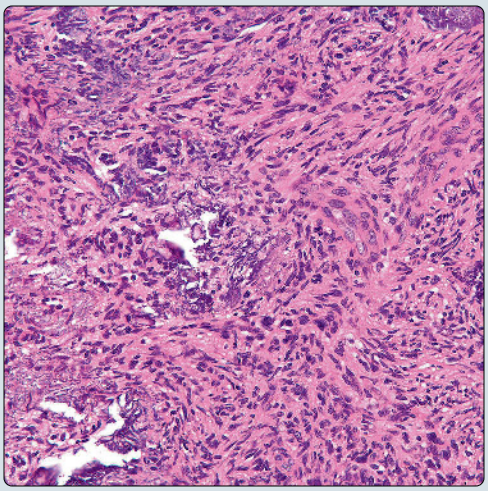


**(Left)** *This patient presented with spontaneous rib fractures and was found to have a small lesion in the femur. The lesion is eccentrically located and well demarcated.* **(Right)** *Low-power view of a phosphaturic mesenchymal tumor is shown. The tumor has replaced the marrow spaces and grows in an infiltrative growth pattern, encasing preexisting trabecular bone. In phosphaturic mesenchymal tumors, this is not diagnostic of malignancy (as in many other primary bone tumors).*

**Well-Demarcated Tumor**



**Grungy Calcifications**



**(Left)** *Phosphaturic mesenchymal tumor is well demarcated from the overlying cortical bone. The solid tumor varies in its degree of cellularity.* **(Right)** *Phosphaturic mesenchymal tumor has heterogeneous histological appearances. The mixed connective tissue type is composed of fascicles of spindle cells and stroma that contains so-called purple "grungy calcifications."*

## TERMINOLOGY

### Abbreviations

- Phosphaturic mesenchymal tumor (PMT)

### Synonyms

- Osteomalacia-associated mesenchymal tumor

### Definitions

- Distinctive mesenchymal tumor associated with oncogenic osteomalacia; osteomalacia is caused by phosphate wasting

## ETIOLOGY/PATHOGENESIS

### Neoplasm

- Neoplastic process many of which show *FN1-FGFR1* or less commonly *FN1-FGF1* gene fusion

## CLINICAL ISSUES

### Epidemiology

- Age
  - Can occur in all age groups (9-80 years)
- Sex
  - Intraosseous PMT is more common in females

### Site

- In largest series published, 2 tumors arose in femur and 1 each in sacrum, phalanx, metacarpal, iliac crest, cervical vertebra, mandible, and tibia

### Presentation

- Bone pain often present for many years; fractures

### Laboratory Tests

- Hypophosphatemia; decreased 1,25-dihydroxyvitamin D3 levels
- Tumors express fibroblast growth factor 23
  - FGF23 inhibits renal tubular phosphate transport and causes phosphate wasting

### Treatment

- Removal of neoplasm; patients do not respond to vitamin D supplementation

### Prognosis

- Most intraosseous PMTs are benign; oncogenic osteomalacia is reversible after removal of tumor

## MACROSCOPIC

### General Features

- Tumors usually small at time of diagnosis and may not be detectable clinically

## MICROSCOPIC

### Histologic Features

- Stellate to spindle-shaped cells
- Myxoid, myxochondroid, chondroid, or osteoid matrix
  - Some of these tumors can resemble chondromyxoid fibroma
- Flocculent calcified matrix often with surrounding osteoclast-type giant cells; prominent vasculature
- Histologically malignant tumors show increased cellularity and mitotic activity and resemble undifferentiated sarcomas
- Microcystic or aneurysmal cone cyst-like changes
- Infiltrative growth pattern with encasement of preexisting trabecular bone can be seen in benign-appearing PMTs and is not indicative of malignancy; malignant variants are very uncommon

## DIFFERENTIAL DIAGNOSIS

### Solitary Fibrous Tumor

- Patternless pattern; prominent hemangiopericytoma-like vascular pattern
- Strongly CD34 and STAT6 positive
- Lacks calcification seen in PMTs

### Giant Cell Tumor of Bone

- Contains osteoclast-type giant cells and fibrohistiocytic areas similar to PMTs
- Osteoclast-type giant cells in giant cell tumor of bone are evenly distributed, and nuclei of giant cells have nuclear features similar to mononuclear neoplastic cells

### Mesenchymal Chondrosarcoma

- Obviously malignant neoplasm
- Composed of round and spindle-shaped cells with chondroid areas and hemangiopericytoma-like vascular pattern

## SELECTED REFERENCES

1. Lee JC et al: Characterization of FN1-FGFR1 and novel FN1-FGF1 fusion genes in a large series of phosphaturic mesenchymal tumors. Mod Pathol. ePub, 2016

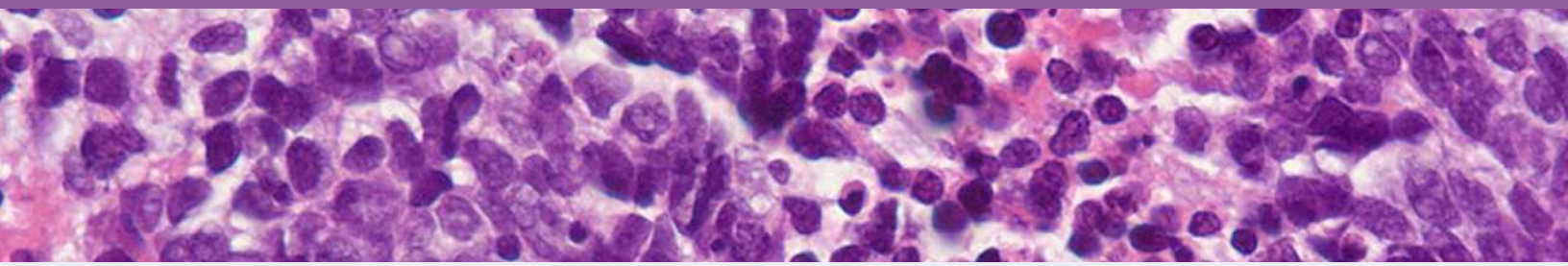
## Immunohistochemistry

| Antibody | Reactivity | Staining Pattern | Comment |
|---|---|---|---|
| FGF23 | Positive | Cytoplasmic | Granular cytoplasmic staining |
| Actin-sm | Positive | Cytoplasmic | Focally positive |
| CD34 | Negative | | |
| S100 | Negative | | |
| Desmin | Negative | | |
| AE1/AE3 | Negative | | |

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SECTION 14

# Metastatic Tumors



Metastatic Tumors **420**

KEY FACTS

## CLINICAL ISSUES

- Metastases are far more common than primary bone tumors (25:1)
- Most common primary sites are lung, breast, prostate, kidney, and thyroid
- Commonly involved bones include skull, spine, ribs, pelvis, humerus, and femur

## IMAGING

- Lesions may be entirely sclerotic or lytic or mixture of sclerotic and lytic
- Typically lytic metastases: Renal cell carcinoma and thyroid carcinoma
- Typically sclerotic metastases: Prostate, breast, and neuroendocrine carcinomas
- PET/CT is very sensitive for detection of bone metastasis

## MICROSCOPIC

- Osteoblastic metastases show abundant reactive woven bone
- Morphology generally resembles primary lesion

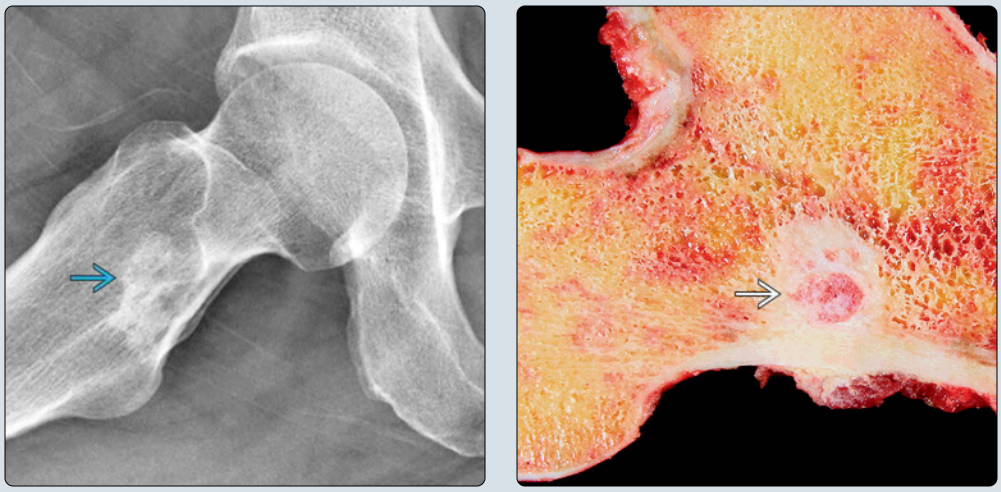
## ANCILLARY TESTS

- Renal cell carcinoma
  - pax-8(+) &/or RCC(+) &/or carbonic anhydrase IX(+)
- Lung adenocarcinoma
  - TTF-1(+) &/or NAPSIN-A(+)
- Breast
  - GATA3(+) &/or mammaglobulin (+) &/or GCDFP-15(+)

## TOP DIFFERENTIAL DIAGNOSES

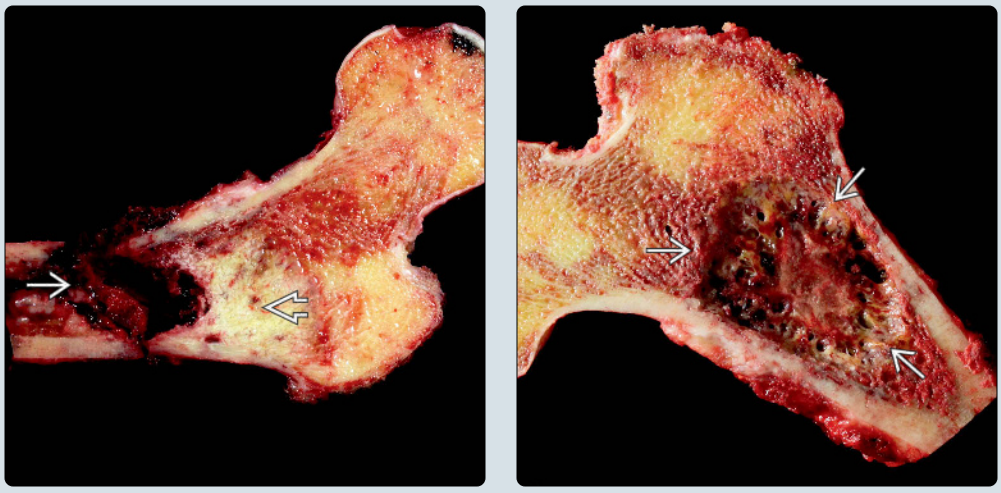
- Osteosarcoma
- Epithelioid vascular tumors

**Sclerotic Metastasis** | **Osteoblastic Metastasis**



**(Left)** *Plain radiograph of the right hip shows a single focus of bony sclerosis in the neck of the femur. Biopsy revealed a metastatic carcinoma. Patient reported a prior history of lobular carcinoma. The immunohistochemical appearance was compatible with a breast primary.* **(Right)** *The resected head of the femur of the same patient is seen. Cross section of the femoral head shows a well-circumscribed osteosclerotic metastasis (breast primary) involving the femoral neck.*

**Pathologic Fracture of Femur** | **Hemorrhagic Renal Cell Carcinoma**



**(Left)** *Pathologic fracture involving the subtrochanteric portion of the femur is shown. On histology, the hemorrhagic lesion showed a metastatic adenocarcinoma. Note the bony sclerosis adjacent to the fracture site.* **(Right)** *A gross image of a metastatic renal cell carcinoma is shown. The well-circumscribed lesion is in the intertrochanteric region of the femur. The tumor was soft and hemorrhagic. The tumor is confined to the intramedullary region. Note the absence of peritumoral sclerosis in the adjacent bone.*

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Metastases are far more common than primary bone tumors (25:1)
  - Most common primary sites are lung, breast, prostate, kidney, and thyroid
    - Other tumors include lymphoma, melanoma, neuroendocrine, and hepatocellular carcinoma
  - After lung and liver, skeleton is 3rd most frequent site of metastatic disease
- Age
  - More common in elderly population

### Site

- Predilection for red marrow; commonly involved bones include skull, spine, ribs, pelvis, humerus, and femur
- Metastases distal to knee and tibia are rare
  - Distal metastases are typically from lung
- In long bones, metastatic deposits tend to involve metaphysis
  - Solitary metastasis in long bones may mimic primary sarcoma

### Presentation

- Pain is typical presenting symptom
- Pathologic fracture

### Laboratory Tests

- Hypercalcemia in patients with extensive metastasis

### Treatment

- Surgical approaches
  - Isolated metastases may be resected
- Radiation
  - May be effective in controlling symptoms
- If patient is asymptomatic, then observation with repeat radiographs may suffice
  - Use of bisphosphonate or RANKL inhibitor should be considered to reduce skeletally related events or fractures

## IMAGING

### Radiographic Findings

- Lesions may be entirely sclerotic, entirely lytic, or combination of both sclerotic and lytic
- Typically lytic metastases
  - Renal cell carcinoma has soap bubble appearance
    - May show aneurysmal bone cyst-like changes
  - Thyroid
- Typically sclerotic metastases
  - Prostate, breast, and neuroendocrine

### CT Findings

- PET/CT is very sensitive for detection of bone metastasis

### Bone Scan

- Hot on bone scan
- Sensitivity: 80-90%
  - More sensitive than plain film or CT

## MICROSCOPIC

### Histologic Features

- Morphology generally resembles primary lesion
  - Adenocarcinoma and squamous cell carcinoma
  - Sarcomatoid carcinoma may resemble primary sarcoma of bone
- Osteoblastic metastasis shows abundant reactive woven bone
  - Unlike osteosarcoma, bone is lined by plump, benign-appearing osteoblasts
- Secondary changes, including hemorrhage, fibrosis, and osteoclast-type giant cell reaction, are common
- Common metastatic lesions in children: Neuroblastoma, rhabdomyosarcoma

## ANCILLARY TESTS

### Immunohistochemistry

- Renal cell carcinoma
  - pax-8(+) &/or RCC(+) &/or carbonic anhydrase IX(+)
- Lung adenocarcinoma
  - TTF-1(+) &/or NAPSIN-A(+)
- Thyroid
  - Thyroglobulin (+) &/or TTF-1(+)
- Prostate
  - PSA(+) &/or PSAP(+)
- Breast
  - GATA3(+) &/or mammaglobulin (+) &/or GCDFP-15(+)
- Epithelioid vascular tumors, osteosarcoma, and adamantinoma are keratin (+) primary bone tumors

## DIFFERENTIAL DIAGNOSIS

### Osteosarcoma

- Osteoblastic metastasis, such as prostatic metastasis, may mimic osteosarcoma
  - Osteosarcoma may be focally positive for keratin
  - Osteosarcoma cells are negative for PSA and PSAP

### Epithelioid Vascular Tumors

- Epithelioid hemangioma, epithelioid hemangioendothelioma, and angiosarcoma may all be diffusely positive for keratin
- All 3 vascular tumors are positive for endothelial cell markers: CD31, CD34, FLI-1, ERG

## DIAGNOSTIC CHECKLIST

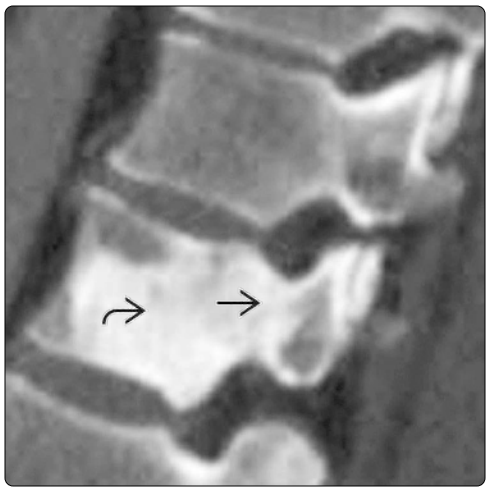
### Pathologic Interpretation Pearls

- Management of metastasis differs significantly from management of primary bone tumor
  - With primary bone tumors, every attempt is made to resect with negative margin
- Frozen section is often requested to exclude diagnosis of metastatic carcinoma
  - When distinction cannot be made, judicious deferral to permanent sections is prudent

## SELECTED REFERENCES

1. Rougraff BT: Evaluation of the patient with carcinoma of unknown origin metastatic to bone. Clin Orthop Relat Res. (415 Suppl):S105-9, 2003

### Osteoblastic Vertebral Metastasis

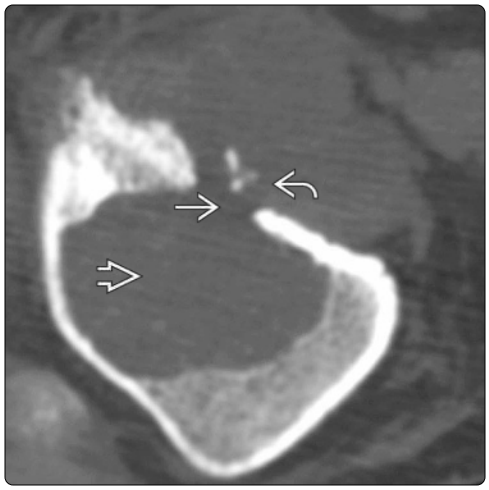


### Osteolytic Metastasis to Neck of Femur

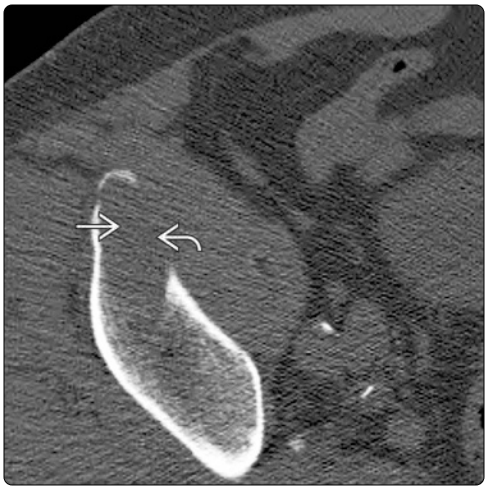


**(Left)** *Plain radiograph shows sclerosis of the body and pedicle of a thoracic vertebra. This lesion represents an osteosclerotic metastasis from a prostatic adenocarcinoma. Other common tumors with sclerotic metastases are breast, neuroendocrine, and some gastrointestinal carcinomas.* **(Right)** *Plain radiograph shows a lytic metastatic breast carcinoma to the femoral neck. The poorly defined margins are concerning for malignant neoplasm. An intratumoral pathologic fracture is present.*

### Osteolytic Femoral Metastasis

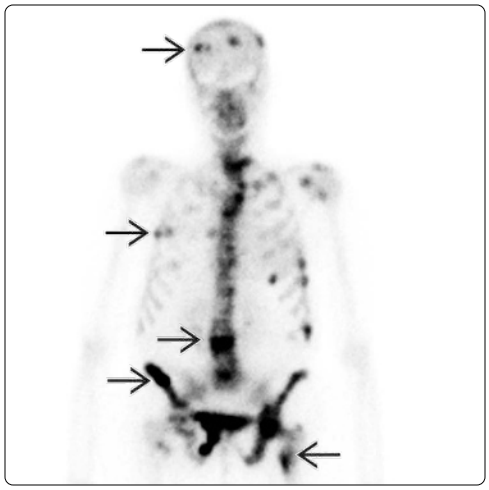


### Osteolytic Metastasis to Pelvis

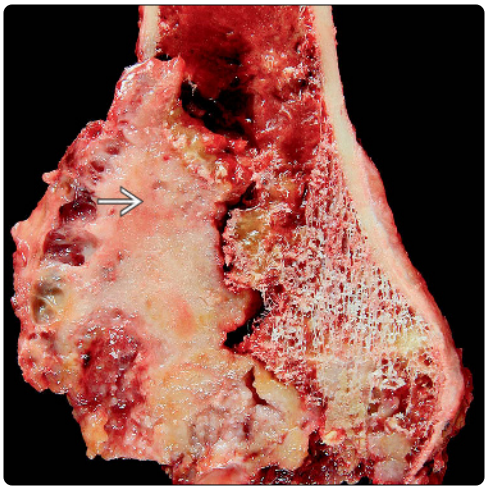


**(Left)** *Axial CT of the femur shows a large intramedullary lytic metastasis with destruction of the cortex. Note also the presence of extraosseous extension. Common malignancies causing osteolytic metastases include renal, lung, and thyroid tumors. The primary lesion in this case was a sacral chordoma.* **(Right)** *Axial CT shows an osteolytic metastasis to the pelvis from a clear cell renal cell carcinoma. Loss of cortex is seen medially. An extraosseous soft tissue mass is not seen.*

### Bone Scan With Multiple Hot Foci

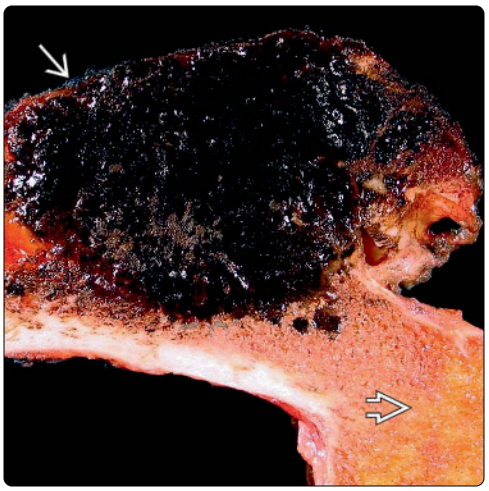


### Metastatic Carcinoma to Femur

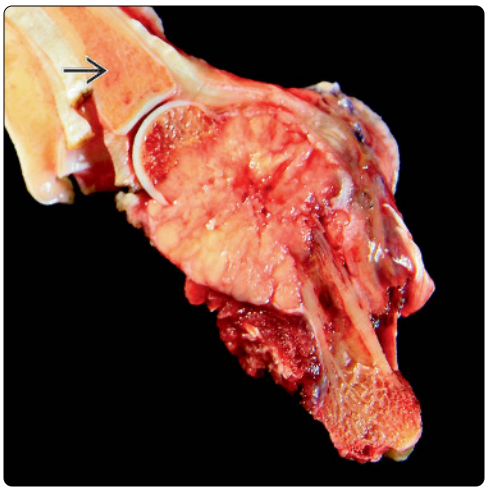


**(Left)** *Bone scan of a woman with breast carcinoma and widespread metastases to bone is shown. Areas of intense radionuclide uptake are seen in the skull, ribs, vertebral column, pelvis, and proximal femur.* **(Right)** *Gross photograph of a resected femur shows a metastasis from a lung carcinoma. An eccentric, predominantly intramedullary destructive lesion is apparent.*

### Metastatic Melanoma to Femur

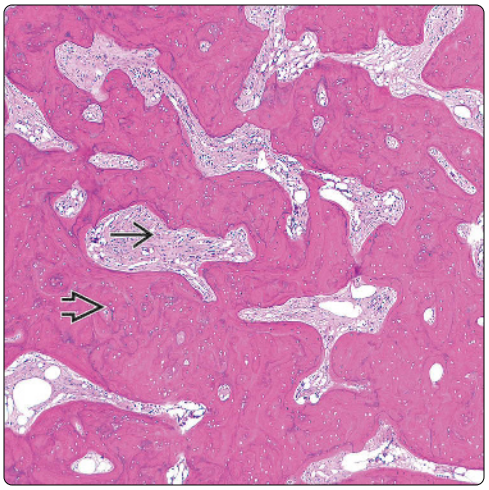


### Metastatic Carcinoma to Metatarsal Bone

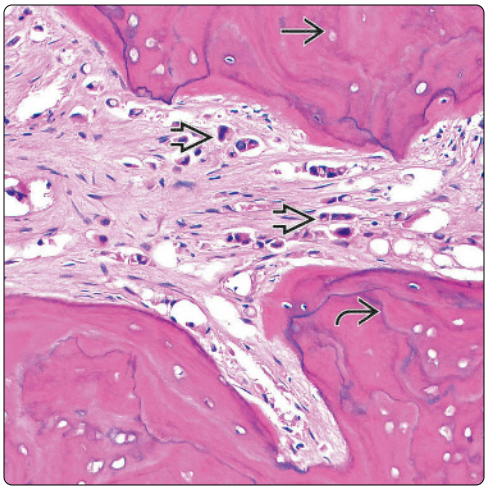


**(Left)** *Gross image shows metastatic melanoma to the proximal portion of the femur ➡. The ink-black color is virtually diagnostic of metastatic melanoma. Rarely, a hemorrhagic metastasis may show a similar gross appearance. The femoral head was free of tumor ➡.* **(Right)** *Gross image shows metastatic renal cell carcinoma to distal portion of metacarpal bone. The expansile gray-white tumor destroys the cortex and forms a soft tissue mass. Note the uninvolved proximal phalanx ⇨. Radiologically, this was a lytic lesion.*

### Osteoblastic Metastatic Breast Carcinoma

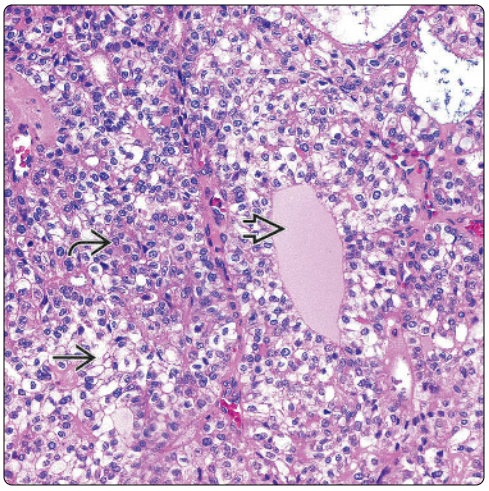


### Osteoblastic Metastatic Breast Carcinoma

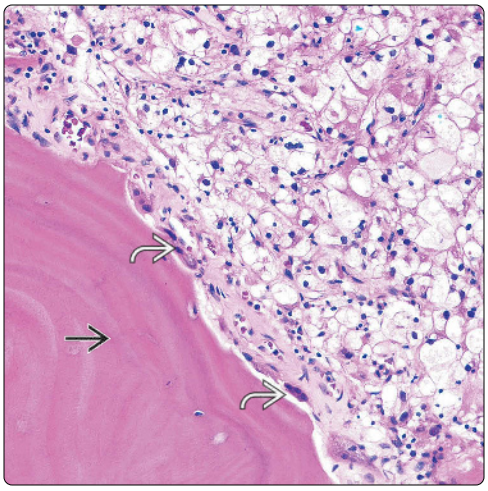


**(Left)** *Low-power photograph shows a resected osteoblastic metastasis (primary in breast). The tumor cells (not easily visualized) are overshadowed by desmoplastic stroma ⇨ and abundant reactive bone ⇨.* **(Right)** *Resected osteoblastic metastasis from a lobular carcinoma of the breast is shown. Reactive woven bone ⇨ shows reversal lines ⇨. Isolated tumor cells are seen ⇨. The tumor cells are surrounded by abundant desmoplastic stroma. The clustering of tumor cells, albeit limited, supports a carcinoma.*

### Metastatic Follicular Carcinoma to Bone

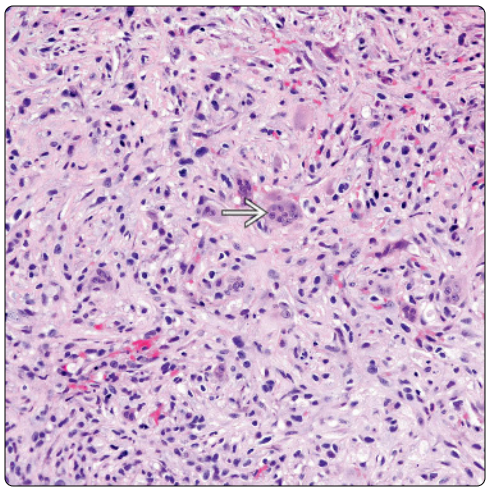


### Metastatic Renal Cell Carcinoma

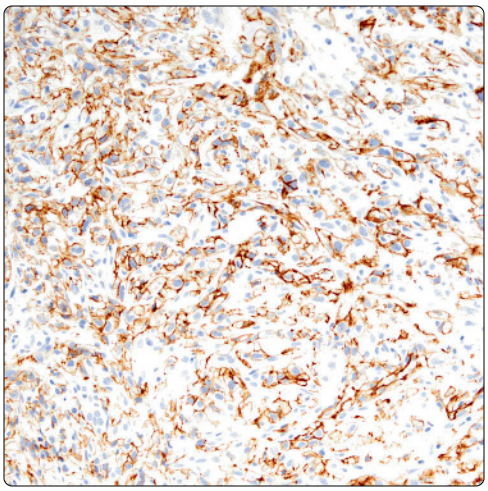


**(Left)** *This photomicrograph of metastatic follicular thyroid carcinoma to bone shows epithelioid tumor cells with cytoplasm varying from clear ⇨ to eosinophilic ⇨. A follicular structure containing pink eosinophilic colloid material is present ⇨.* **(Right)** *Metastatic renal cell carcinoma, clear cell type, shows preexisting lamellar bone ⇨ rimmed with osteoclasts ➡. The tumor cells show a low nuclear:cytoplasmic ratio and abundant clear cytoplasm. Note the tumor cells show only low-grade nuclear atypia.*

## Metastatic Sarcomatoid Carcinoma

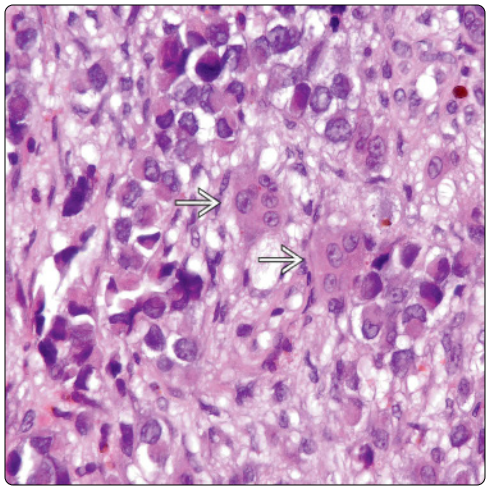


## Positive Carbonic Anhydrase IX Stain

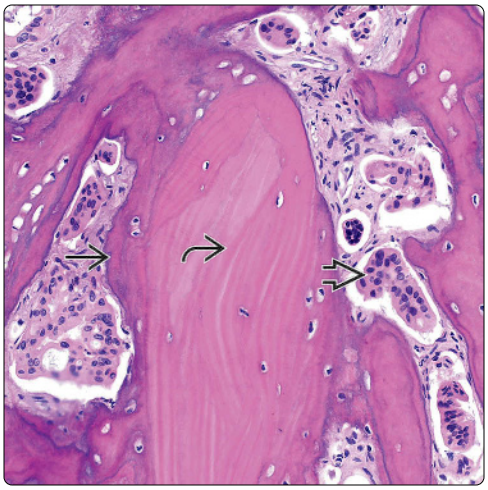


**(Left)** *Metastatic sarcomatoid renal cell carcinoma to rib is shown. The lack of cohesive nests of tumor cells and their spindled character raises the possibility of a primary sarcoma. On immunohistochemistry, the tumor cells were positive for keratin and carbonic anhydrase IX. Osteoclast-type giant cell are present.* **(Right)** *Photomicrograph of a metastatic sarcomatoid renal cell carcinoma to rib diffusely positive for carbonic anhydrase IX is shown. The tumor cells were also positive for keratin.*

## Osteoclast-Type Giant Cells

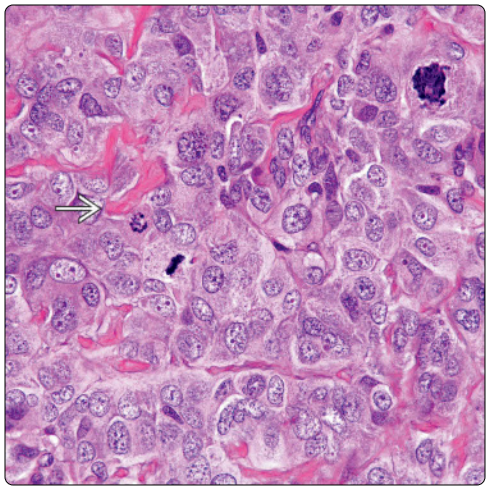


## Osteoblastic Metastasis From Pancreas

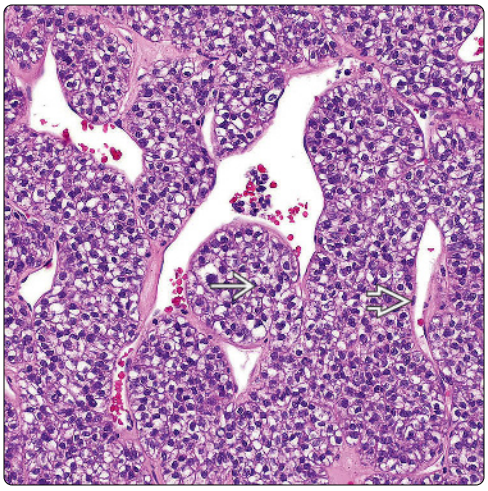


**(Left)** *Metastatic mammary carcinoma to bone is shown. Although the cells are epithelioid, there is a distinct lack of cohesive tumor cells. Also note the osteoclast-type giant cells. The lack of resemblance between the nuclei of the giant cells and tumor cells argues against a giant cell tumor of bone.* **(Right)** *Metastatic pancreatic carcinoma to bone is shown. Thick seams of woven bone are seen buttressing preexisting lamellar bone. Metastatic carcinoma is seen between seams of bone.*

## Epithelioid Osteosarcoma of Bone

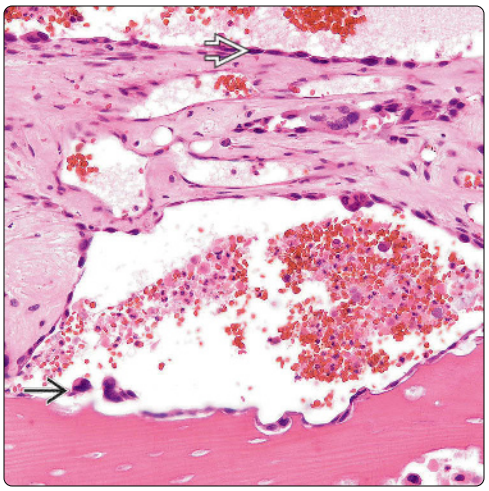


## Metastatic Hepatocellular Carcinoma

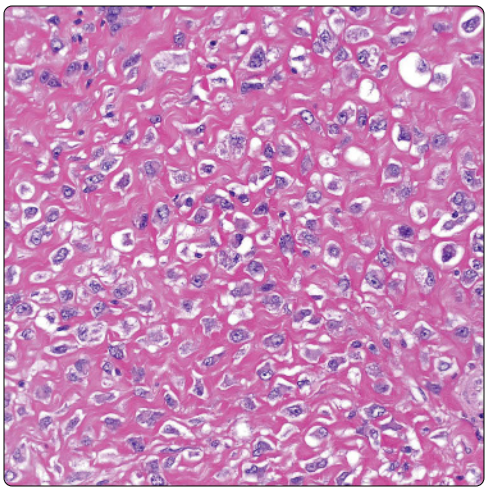


**(Left)** *Metastatic epithelioid osteosarcoma is shown. The epithelioid nature of the tumor cells, the somewhat cohesive organization, and lack of osteoid are concerning for a metastatic carcinoma. Delicate collagen is noted. Osteoid was identified elsewhere on the slide.* **(Right)** *Metastatic hepatocellular carcinoma to bone is shown. The tumor demonstrates a macrotrabecular pattern, and the trabeculae are encased by endothelial cells. Note the abundant clear cytoplasm.*

### Pseudovascular Spaces

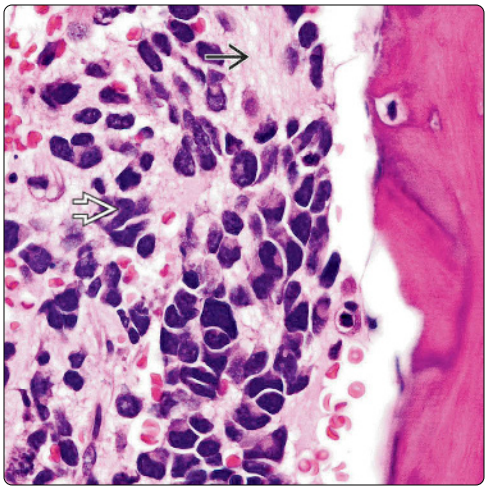


### Sclerosing Epithelioid Fibrosarcoma

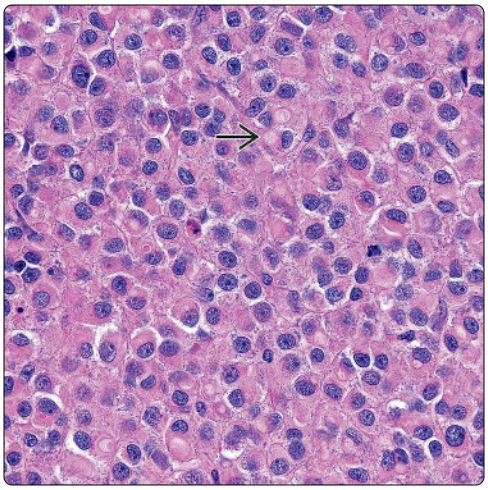


**(Left)** *A metastatic urothelial carcinoma to bone is illustrated. The cystic spaces mimic an angiosarcoma. The tumor cells ⇒ were strongly positive for keratin and negative for endothelial cell markers. Osteoclastic activity is also seen ⇨. (Right) The epithelioid cells are surrounded by a dense collagenous stroma. These tumors may be positive for keratin and EMA and thus mimic a metastatic carcinoma. Sclerosing epithelioid fibrosarcomas are characteristically positive for MUC4.*

### Metastatic Neuroblastoma to Bone

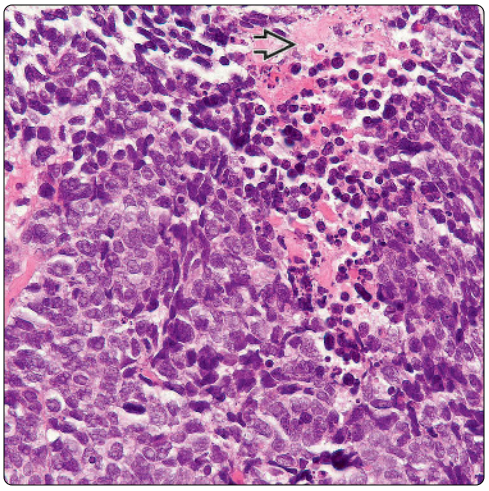


### Metastatic Mammary Lobular Carcinoma

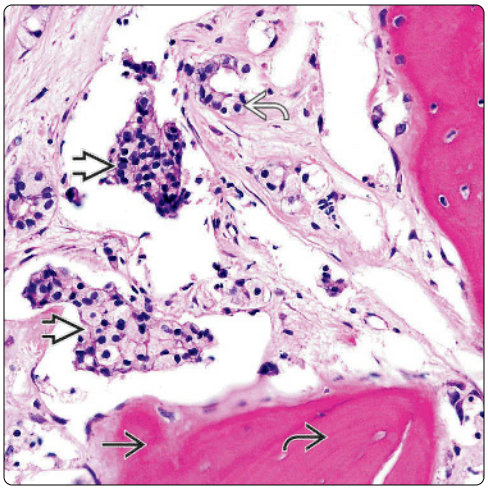


**(Left)** *This photomicrograph of metastatic neuroblastoma to bone shows a small round blue cell tumor ⇒. Although this appearance raises a wide differential diagnosis, the fibrillary neuropil ⇨ seen in the background assists in narrowing the differential diagnosis.* **(Right)** *Metastatic lobular breast carcinoma to bone shows monotonous tumor cells with abundant eosinophilic cytoplasm. Intracytoplasmic vacuoles ⇨ (targetoid appearance) are characteristic of this tumor. The differential diagnosis includes plasmacytoma.*

### Metastatic Small Cell Carcinoma to Bone



### Metastatic Prostatic Carcinoma to Bone



**(Left)** *This metastatic small cell carcinoma to bone shows hyperchromatic nuclei with prominent nuclear molding. Zones of necrosis are also seen ⇨. Common sites of origin of small cell carcinoma include lung and, less commonly, gastrointestinal tract.* **(Right)** *Metastatic prostate carcinoma, osteoblastic type, shows lamellar bone ⇨ encased by reactive woven bone ⇨. The tumor cells are monomorphic with clear cytoplasm ⇨. Acinar differentiation ⇒ in the form of small glands is present focally.*

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SECTION 15

# Bone Tumor Mimics




| | |
|---|---|
| Bizarre Parosteal Osteochondromatous Proliferation and Related Lesions | **428** |
| Melorheostosis | **434** |
| Amyloidoma | **438** |
| Gaucher Disease | **440** |

KEY FACTS

## TERMINOLOGY

- Benign, matrix-producing proliferative process that arises on surfaces of bone mimics other neoplasms clinically, radiologically, and pathologically

## ETIOLOGY/PATHOGENESIS

- Bizarre parosteal osteochondromatous proliferation (BPOP) and subungual exostosis have associated translocations; likely neoplasms

## CLINICAL ISSUES

- Uncommon: Exact incidence not known
- Typically develops on surfaces of short tubular bones of hands and feet
- 75% involve small bones of hands and feet
- 25% arise on long bones of both upper and lower extremities
- Sometimes painful and rapidly growing

## MACROSCOPIC

- Similar to osteochondroma grossly with bony stalk and cartilaginous cap
- Range in size from 0.5-2 cm

## MICROSCOPIC

- Composed of fibrous tissue, bone, and cartilage
- Cartilage undergoes endochondral ossification forming trabeculae woven bone trabeculae rimmed by osteoblasts
- Fibrous tissue may be hypercellular (sometimes absent)

## TOP DIFFERENTIAL DIAGNOSES

- Osteochondroma
- Parosteal osteosarcoma

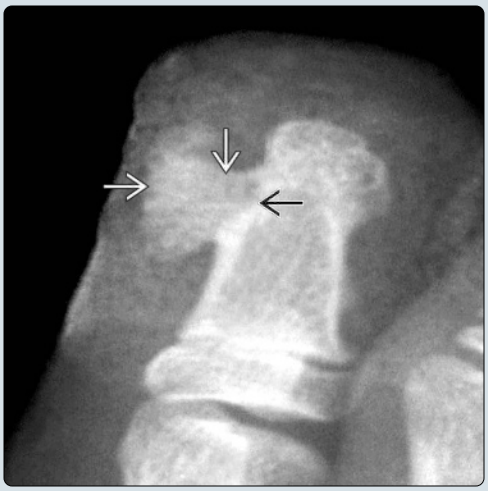
## DIAGNOSTIC CHECKLIST

- Small, quickly growing, surfaces of short tubular bones
- Cellular fibrous tissue overlying hyaline cartilage cap undergoing enchondral ossification

**Ulcerated and Hemorrhagic Mass**



**Mass Displacing Nail**

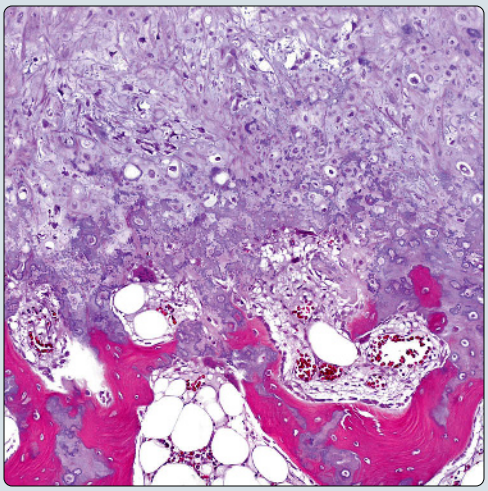


**(Left)** *Subungual exostosis arising beneath the toenail displaces the nail and causes ulceration of the nail bed and adjacent skin. This results in hemorrhage and possibly secondary infection.* **(Right)** *Thick, mineralized new bone ⇨ extends from the surface of the 1st distal phalanx perpendicular to the cortex and forms a mushroom-shaped mass. The endosteal cortex is intact ⇨. The mass displaces the overlying nail.*

**Mass Anchored to Calcaneus**



**Enchondral Ossification**



**(Left)** *The bizarre parosteal osteochondromatous proliferation (BPOP) is anchored to the ventral cortical surface of the calcaneus. The mineralized tumor is oblong with a thick stalk, and the overlying cortex is intact and sclerotic.* **(Right)** *The hyaline cartilage surface of BPOP is moderately cellular and undergoes enchondral ossification, producing trabeculae of bone rimmed by osteoblasts.*

## TERMINOLOGY

### Abbreviations

- Bizarre parosteal osteochondromatous proliferation (BPOP)

### Synonyms

- Nora lesion
- Subungual exostosis and florid reactive periostitis are similar processes

### Definitions

- Benign, matrix-forming proliferative process beneath periosteum on bone surface

## ETIOLOGY/PATHOGENESIS

### Reactive Process

- Florid reactive periostitis may be related to trauma

### Genetic Factors

- BPOP: t(1;17); subungual exostosis: t(X;6)
- Florid reactive periostitis: No reported genetic aberrations

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Rare; exact incidence not known
- Age
  - Adolescence through mid adulthood
- Sex
  - Equal gender distribution

### Site

- Surfaces of short tubular bones of hands and feet
  - Small bones of hands and feet (75%)
  - Long bones of upper and lower extremities (25%)
- Usually diaphysis or metaphysis
- Subungual exostosis develops beneath nail bed
  - Great toe (70-80%) followed by thumb and index finger

### Presentation

- Mass; painful in minority of cases
- Subungual exostosis distorts nail; pain, bleeding
- Sometimes rapidly growing

### Natural History

- Limited growth potential; ossifies with time

### Treatment

- No treatment necessary in asymptomatic patients
- Usually treated by simple excision

### Prognosis

- Recurrences common, developing in 50% of cases
- Reexcision often curative

## IMAGING

### Radiographic Findings

- Well delineated, pedunculated, and nodular
- Cap has features of cartilage
- Surface based and radiodense
  - Initially radiolucent, becomes radiodense over time
- Cortex intact; no continuity with medullary cavity

### MR Findings

- Cartilage cap bright on T2-weighted images

## MACROSCOPIC

### General Features

- Hard, polypoid, well defined, tan-white
  - Fibrous tissue overlying cartilage with attached bone

### Size

- 0.5-2 cm; most 1 cm

## MICROSCOPIC

### Histologic Features

- Composed of 3 different components
  - Fibrous tissue, cartilage, and bone
- Fibrous tissue may be hypercellular (sometimes absent)
  - Fibroblasts arranged in short, intersecting fascicles and have ill-defined eosinophilic cytoplasm and elongate nuclei with fine chromatin
- Hyaline cartilage hypercellular; large cells, plump nuclei, binucleation common
- Cartilage undergoes endochondral ossification forming trabeculae of woven bone rimmed by prominent osteoblasts
  - Bone attached to underlying intact cortex
- Mitoses may be numerous but are not atypical
- Florid reactive periostitis often lacks cartilage

## DIFFERENTIAL DIAGNOSIS

### Osteochondroma

- Radiology helpful; continuity with medullary cavity and center of lesion; underlying cortex intact in BPOP, subungual exostosis, and florid reactive periostitis
- Cartilage resembles disorganized growth plate; not seen in BPOP and subungual exostosis
- Lacks hypercellular fibrous component

### Parosteal Osteosarcoma

- Rarely arises on small bones of hands and feet
- Atypical spindle cells oriented around long trabeculae of tumor bone; absent in BPOP, subungual exostosis, and florid reactive periostitis
- Amplification of MDM2

## DIAGNOSTIC CHECKLIST

### Clinically Relevant Pathologic Features

- Small, quickly growing, surfaces of short tubular bones

### Pathologic Interpretation Pearls

- Cellular fibrous tissue overlying hyaline cartilage cap undergoing enchondral ossification

## SELECTED REFERENCES

1. Soni A et al: Florid reactive periostitis ossificans of the humerus: case report and differential diagnosis of periosteal lesions of long bones. World J Orthop. 6(7):559-63, 2015
2. Meneses MF et al: Bizarre parosteal osteochondromatous proliferation of bone (Nora's lesion). Am J Surg Pathol. 17(7):691-7, 1993

**BPOP of Distal Phalanx**



**Multinodular Mass**



**(Left)** *Radiograph of BPOP shows a mixed lucent and blastic lesion on the ventral surface of the distal phalanx with a thin shell of periosteal new bone. Distally, the periosteal bone forms an overhanging edge and extends proximally.* **(Right)** *BPOP has a multinodular configuration and extends into the soft tissues from the dorsal surface of the metacarpal. The lesion is composed of several bridging masses. The bone has a fine trabecular pattern. The underlying cortex is intact.*

**Large BPOP**



**Florid Reactive Periostitis**



**(Left)** *This BPOP of the volar aspect of the proximal phalanx is more sessile in shape. The mass has an undulating contour and is anchored to the intact underlying cortex.* **(Right)** *The middle phalanx of the hand is affected by florid reactive periostitis. There is swelling of the finger caused by symmetrical mineralized periosteal new bone deposited on the cortex in a circumferential fashion. The underlying cortex is intact.*

**Mass Near Joint**



**Eccentric Subungual Exostosis**



**(Left)** *Polypoid BPOP arises from the distal surface of the dorsal cortex of the phalanx and displaces the overlying soft tissue and skin. The mass has a trabecular pattern and is based on the underlying sclerotic cortex.* **(Right)** *This subungual exostosis is eccentric and underlies a portion of the nail. The mass is smooth surfaced and has a homogeneous pattern of mineralization.*

Mass Attached to Ilium



Mass Anchored to Femoral Cortex



**(Left)** *Axial CT shows BPOP manifesting as a nodular mass ➡ of periosteal new bone that extends from the posterior surface of the cortex and is connected to it by a stalk ➡. The density of the mass resembles fine trabecular bone.* **(Right)** *Sagittal CT shows a BPOP arising from the proximal femur ➡ that is nodular and composed of fluffy trabecular periosteal new bone. The lesion is anchored to the cortex and extends into the soft tissues. The margins are fairly well defined.*

Recurrent Subungual Exostosis

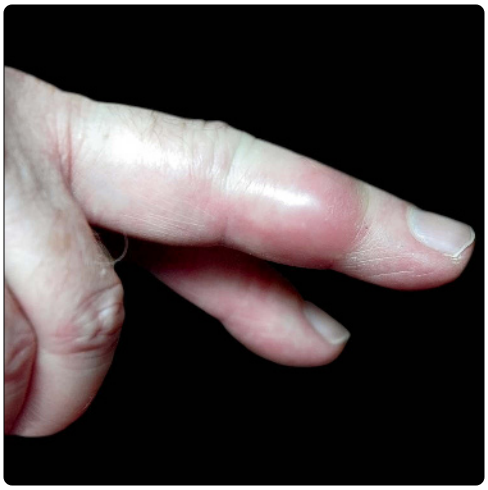


Recurrent Mineralized Mass

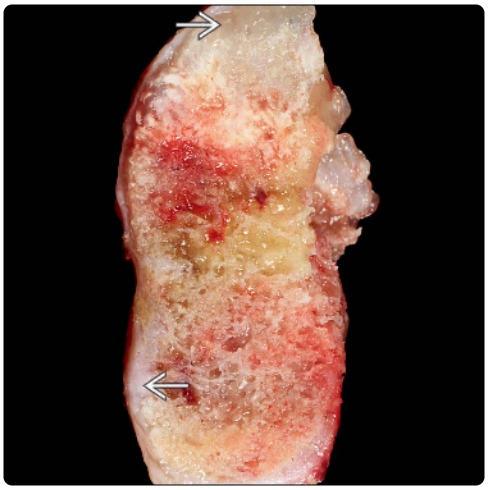


**(Left)** *Subungual exostosis recurs in many cases. The features of the recurrence are similar to that of the primary lesion in that the mass is mushroom-shaped, mineralized, and anchored to the dorsal cortex beneath the nail.* **(Right)** *This recurrent BPOP ➡ is oblong, well defined, mineralized, and has a fine trabecular pattern in areas. The lesion is firmly attached to the underlying cortex, which is intact.*

Swollen Finger

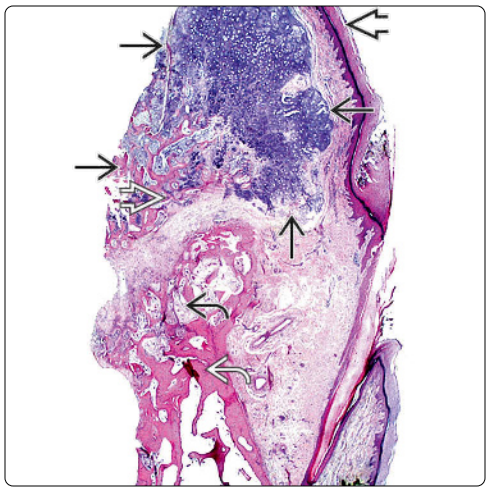


Recurrent Mass

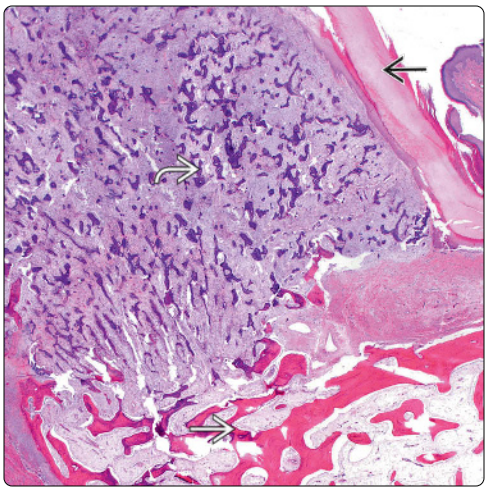


**(Left)** *Florid reactive periostitis presents in this patients as a painful, erythematous, swollen finger. The bulging lesion distorts the overlying skin, which has lost its normal creases.* **(Right)** *Gross photo of resected recurrent BPOP ➡ shows a surface cartilaginous cap that has undergone extensive endochondral ossification, forming the majority of the tumor.*

**Large Mass**

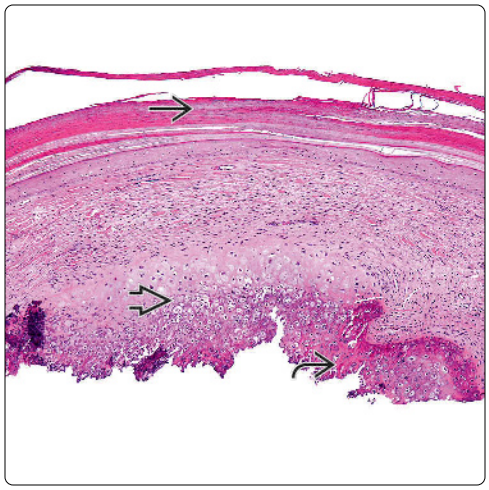


**Nail Displaced by Mass**

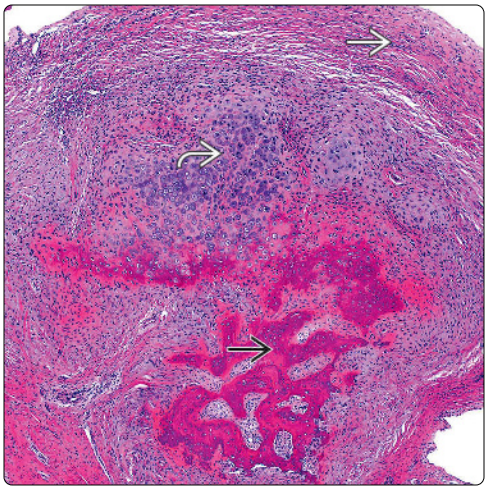


**(Left)** *Toe amputated for subungual exostosis arising beneath the toenail shows the nodular mass that displaces the overlying skin . The mass has a prominent cartilaginous cap that undergoes endochondral ossification . The base of the lesion is anchored to the underlying cortex of the phalanx.* **(Right)** *The subungual exostosis displaces the nail . The mass is anchored to the cortex of the distal digit . Much of the lesion is composed of purple-staining trabecular bone forming a complex network.*

**Shave Excision**

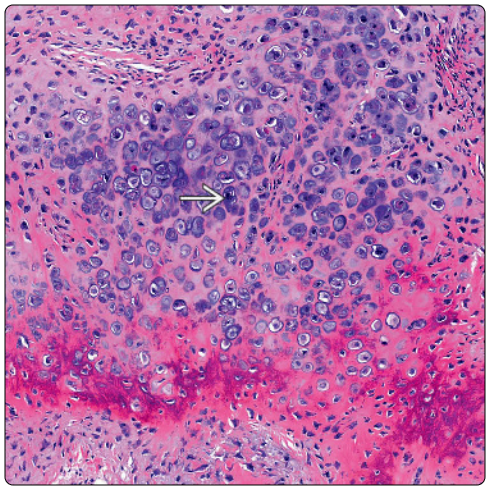


**Cellular Hyaline Cartilage**

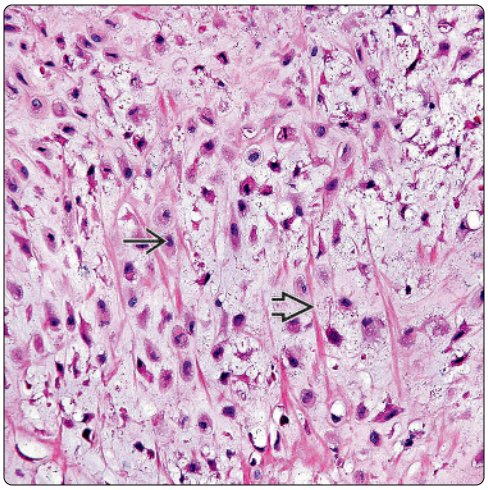


**(Left)** *Shave biopsy of BPOP is surfaced by keratinized squamous epithelium . The outer layer of the mass is covered by reactive fibrous tissue beneath which is a layer of cellular cartilage , and at its base it mineralizes and undergoes endochondral ossification .* **(Right)** *In this example of BPOP, the fibrous tissue component covers the cap of hyaline cartilage that is very cellular . The cartilage undergoes enchondral ossification, forming irregular interconnecting trabeculae of woven bone .*

**Cellular Cartilage and Bone**

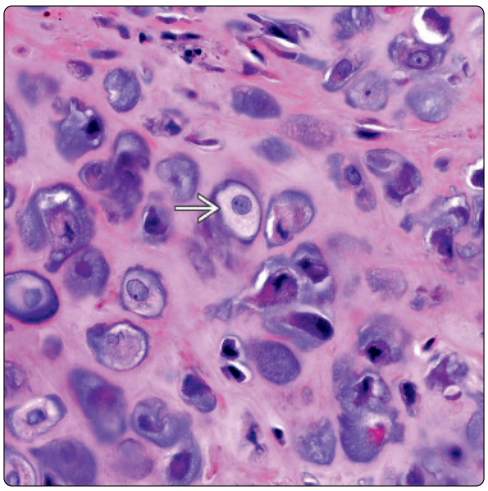


**Cartilage Cap With Large Chondrocytes**

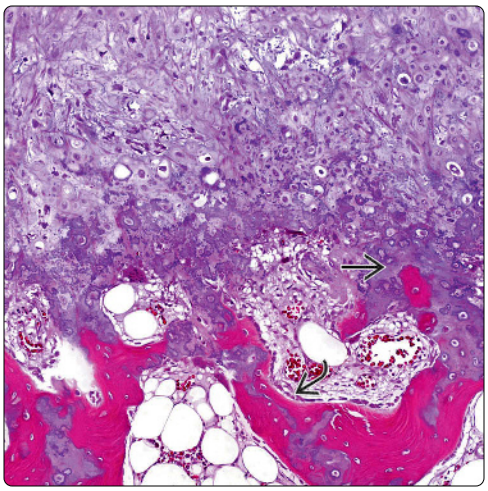


**(Left)** *Cartilage cap of BPOP/subungual exostosis contains plump chondrocytes with enlarged nuclei and small nucleoli. The cartilage merges with reactive bone at the periphery.* **(Right)** *Hypercellular cartilage cap of BPOP contains large chondrocytes . The chondrocyte nuclei have fine chromatin and small nucleoli. Coursing throughout the basophilic matrix are eosinophilic bundles of collagen . The cellularity of the cartilage can cause confusion with chondrosarcoma.*

### Cellular Cartilage Cap

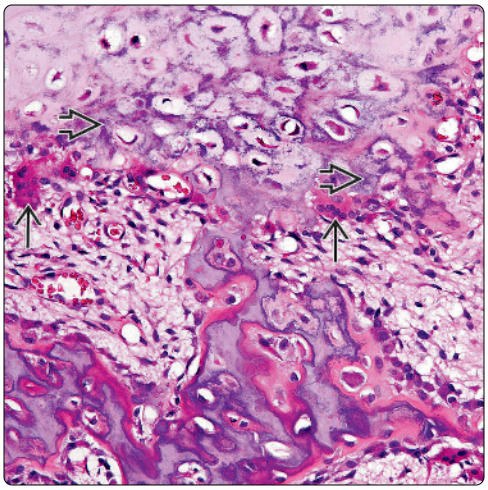


### Enchondral Ossification

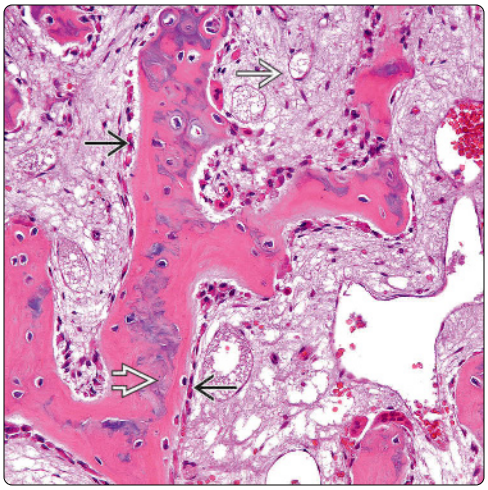


**(Left)** *Hypercellular reactive hyaline cartilage on the surface of BPOP and subungual exostosis is shown. The chondrocytes are enlarged and metabolically active. Note the small nucleoli.* **(Right)** *BPOP and subungual exostosis have a cartilage cap that undergoes enchondral ossification. The base of the cartilage calcifies and undergoes necrosis and resorption by osteoclasts. Residual struts remain to serve as scaffolding for the deposition of bone by osteoblasts.*

### Base of BPOP

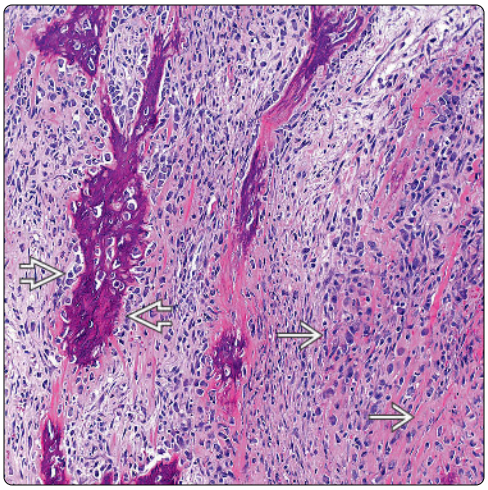


### Stalk of BPOP

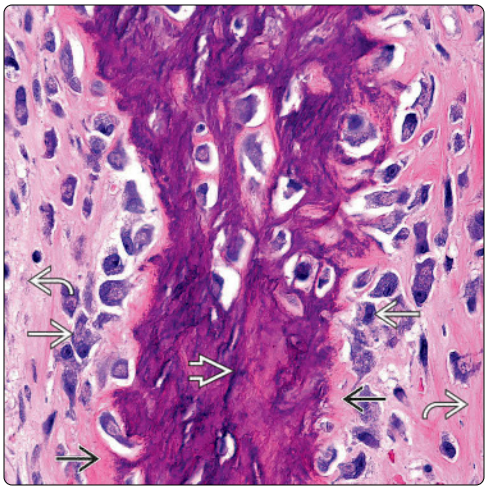


**(Left)** *The base of the cartilage cap in BPOP calcifies before it it is resorbed by osteoclasts. The calcium manifests as small, irregular, purple particles. Residual struts of cartilage act as templates for the newly formed bone.* **(Right)** *This stalk of BPOP is composed of reactive woven trabecular bone that is rimmed by osteoblasts. The intertrabecular space is filled with reactive connective tissue and fat. The central cores of cartilage progressively diminish in volume toward the cortex.*

### Cellular Woven Bone



### Reactive Woven Bone



**(Left)** *Florid reactive periostitis is composed of reactive fibrous tissue and trabecular woven bone. The trabeculae are deposited in parallel array and are in different stages of maturation with the most recently formed being more ill defined. The more mature bone is rimmed by prominent osteoblasts.* **(Right)** *Florid reactive periostitis contains reactive woven bone rimmed by large active osteoblasts. The unmineralized bone (osteoid) is pink whereas the mineralized bone is purple. The bone is surrounded by reactive fibrous tissue.*

# Melorheostosis

KEY FACTS

## TERMINOLOGY

- Rare nonhereditary disease characterized by localized diffuse thickening of cortical bone

## ETIOLOGY/PATHOGENESIS

- Genetic

## IMAGING

- Often likened to wax dripping down surface of bone (dripping candle wax pattern)

## MACROSCOPIC

- Cortex is thickened and irregular

## MICROSCOPIC

- Thickened cortical bone composed of woven and lamellar bone

## TOP DIFFERENTIAL DIAGNOSES

- Camurati-Engelmann disease (progressive diaphyseal dysplasia)
  - Radiographically, does not show dripping candle features seen in melorheostosis
- Ribbing disease (hereditary multiple diaphyseal sclerosis)
  - Affects diaphyses of long bones (e.g., femur and tibia) with no involvement of cortex
- Intramedullary osteosclerosis
  - No cortical thickening
- Paget disease of bone
  - Usually involves entire bone and not just cortex
- Osteoma
  - May share similar radiographic features but is more localized
- Low-grade osteosarcoma
  - Not as homogeneously radiodense and has fibroblastic component

**Dripping Candle Wax Pattern**



*Radiograph of the tibia in a patient with melorheostosis demonstrates the characteristic dripping candle wax pattern of dense compact bone deposited on the surface of the fibula. The tibia is normal.*

**Dense Surface Lesion**



*Radiograph shows the femur in a patient with melorheostosis who has lesions in the pelvis as well. The oblong mass is well demarcated and can mimic osteoma and parosteal osteosarcoma radiographically.*

## TERMINOLOGY

### Synonyms

- Leri disease, flowing periosteal hyperostosis

### Definitions

- Rare nonhereditary disease characterized by localized diffuse thickening of cortical bone
- Frequently associated with scleroderma-like skin changes and vascular lesions, such as arteriovenous and lymphatic malformations

## ETIOLOGY/PATHOGENESIS

### Genetic Disease

- Nonhereditary, sporadic disease; some are associated with germline alterations in *LEMD3* gene in patients who also have osteopoikilosis; it is not found in pure sporadic melorheostosis

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Very rare disorder; no gender predisposition
- Age
  - Usually presents in teenagers or early adulthood

### Site

- Can involve 1 bone (monostotic), multiple bones (polyostotic or polymelic); multiple bones in extremity (monomelic)
- Affects both endosteal and periosteal surfaces of bones, occurs in dermatomal distribution
- Involvement of axial skeleton is rare; does not affect craniofacial skeleton

### Presentation

- Pain, deformities, limb length discrepancy, limitation of motion due to reactive soft tissue fibrosis

### Natural History

- Slowly progressive, stabilizes in adults

### Treatment

- No curative treatment available, only symptomatic treatment, aimed at reducing pain and stiffness

## IMAGING

### Radiographic Findings

- Thickened cortex
- Undulation appearance along cortex
  - Often likened to wax dripping down surface of bone (dripping candle wax pattern)

### MR Findings

- Sclerotic bone shows low signal intensity on T1-weighted images
- On T2-weighted images, sclerotic areas show decreased signal intensity
  - No marked marrow edema or destructive changes; associated soft tissue mass may show high signal intensity

### CT Findings

- Dense cortical sclerosis
- Soft tissue mass may be associated with abnormal bone

### Bone Scan

- Mild to moderate uptake on bone scan

## MACROSCOPIC

### General Features

- Cortex is thickened and irregular

## MICROSCOPIC

### Histologic Features

- Thickened cortical bone composed of woven and lamellar bone
- Subcutaneous and paraarticular fibrosis and calcification may be present

## DIFFERENTIAL DIAGNOSIS

### Camurati-Engelmann Disease (Progressive Diaphyseal Dysplasia)

- Autosomal dominant with onset in childhood
- Characterized by symmetrical and bilateral distribution
- Involves long tubular bones and bones formed by intramembranous ossification, e.g., skull
- Radiographically, does not show dripping candle features seen in melorheostosis

### Ribbing Disease (Hereditary Multiple Diaphyseal Sclerosis)

- Affects diaphyses of long bones (e.g., femur and tibia) with no involvement of cortex
- Usually starts after puberty
- Autosomal recessive

### Intramedullary Osteosclerosis

- No cortical thickening
- Most commonly affects mid tibia

### Paget Disease of Bone

- May be sclerotic and hot on bone scan; usually involves entire bone and not just cortex

### Osteoma

- May share similar radiographic features but is more localized

### Low-Grade Osteosarcoma

- Not as homogeneously radiodense and has fibroblastic component
- Associated with *MDM2* amplification

## DIAGNOSTIC CHECKLIST

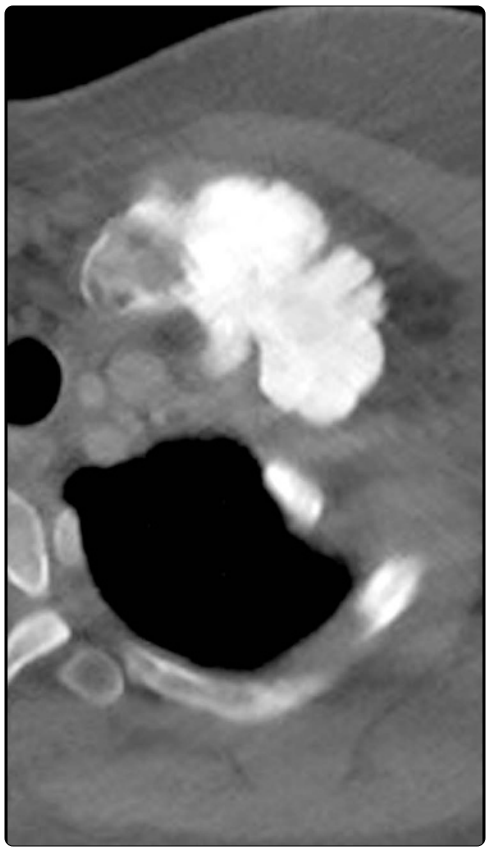
### Pathologic Interpretation Pearls

- Melorheostosis is primarily radiographic diagnosis and need not (and should not) be biopsied

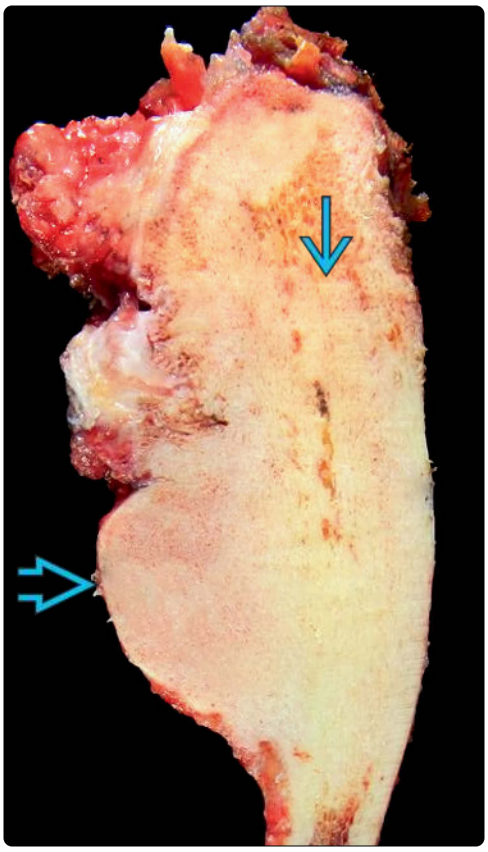
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1. Gagliardi GG et al: Melorheostosis: a literature review and case report with surgical considerations. J Foot Ankle Surg. 49(1):80-5, 2010

**Melorheostosis Arising in Clavicle**

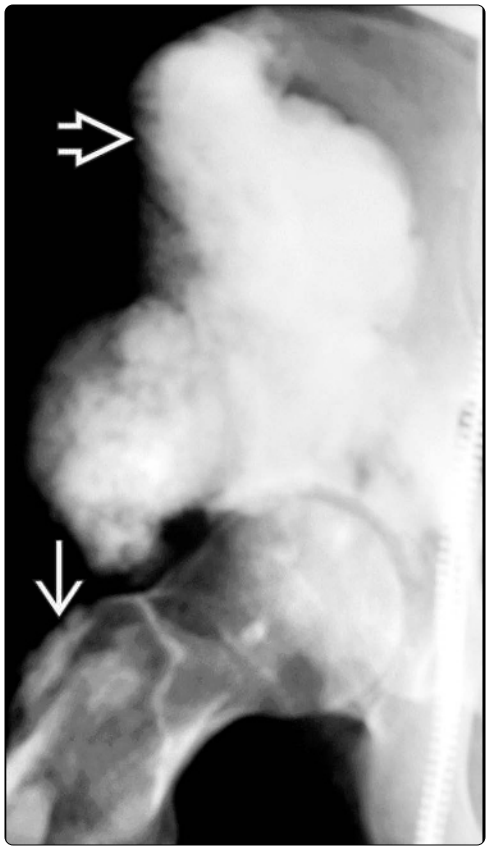


**Gross Photograph of Melorheostosis**

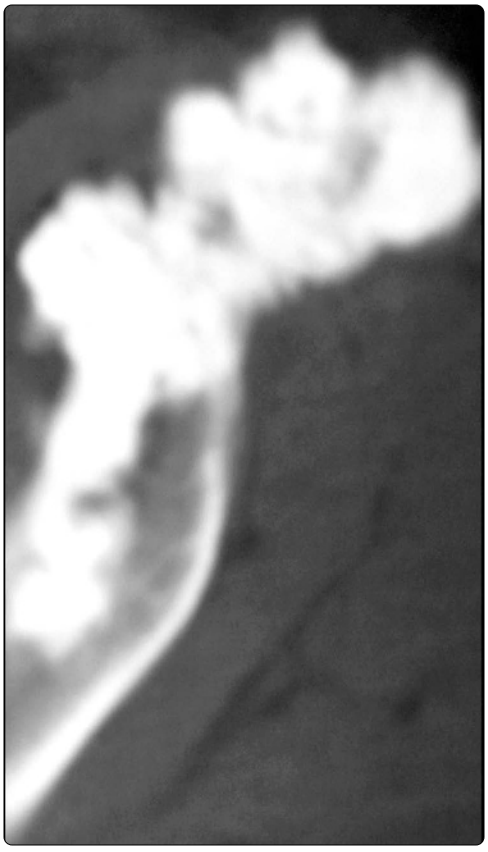


**(Left)** *Melorheostosis arising in the clavicle is shown. There is a sclerotic, lobulated expansile lesion arising in the medial portion of the left clavicle involving the head of the clavicle and medial aspect of the manubrium. The lesion appears to predominantly involve the surface of the bone.* **(Right)** *The corresponding gross resection specimen of the melorheostosis arising in the distal clavicle demonstrates an extensively sclerotic lesion. The lesion is oblong, lobulated, and involves the medullary cavity and adjacent soft tissue.*

**Melorheostosis of Pelvis and Femur**

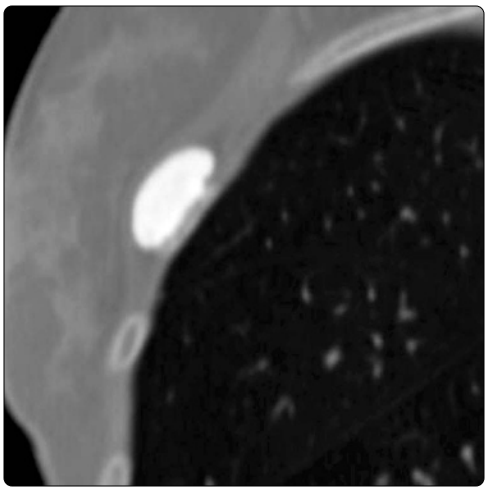


**CT Scan of Melorheostosis of Pelvis**

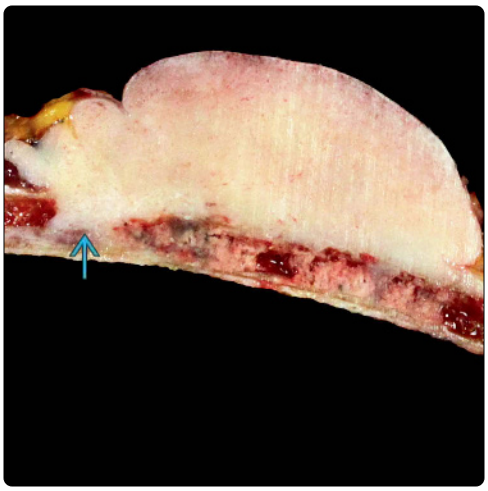


**(Left)** *AP view of the pelvis in a patient with melorheostosis shows radiodense lesions involving the ilium and proximal femur. Both lesions have a cloud-like appearance and involve the surfaces of the bone and also the underlying medullary cavities.* **(Right)** *Axial CT of a lesion in melorheostosis demonstrates a multinodular mass that predominantly involves the surface of the ilium but also the underlying medullary cavity of the bone.*

Melorheostosis of Rib

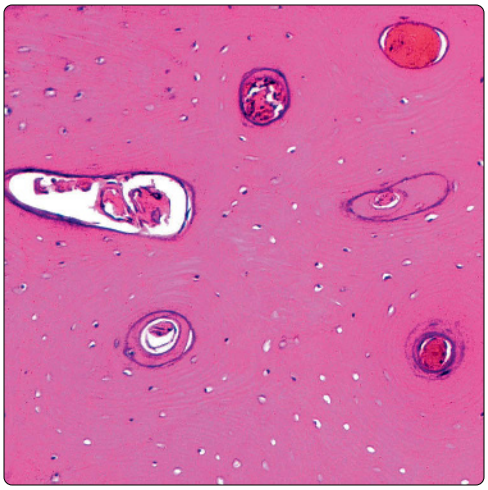


Melorheostosis of Rib

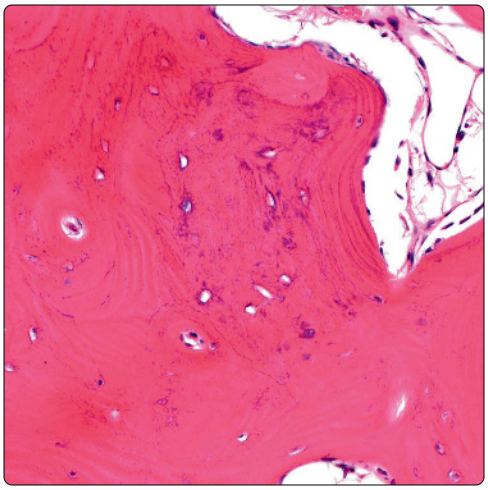


**(Left)** *Melorheostosis arising in the rib is shown. The lesion is extensively sclerotic and appears to predominantly involve the surface of the rib with possible involvement of the underlying medullary cavity.* **(Right)** *Corresponding resection specimen shows the sclerotic lesion arising in the rib. The lesion is predominantly on the surface but focally extends into the underlying medullary cavity* ⇨.

Cortical Type Bone

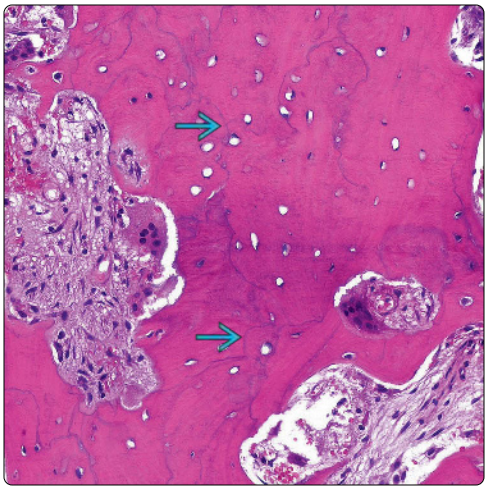


Light Microscopy of Melorheostosis

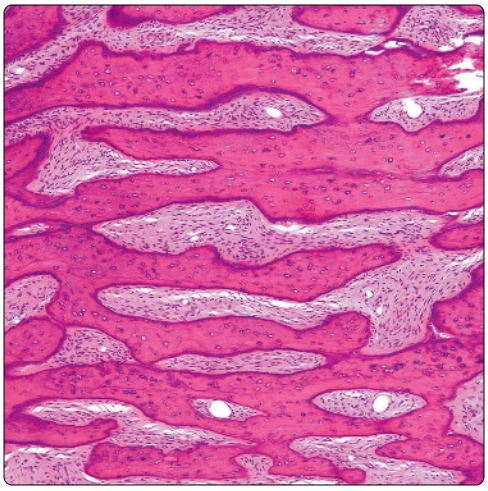


**(Left)** *The lesions of melorheostosis are composed of dense cortical-like bone that is lamellar or lamellar and woven bone. Without correlation to the radiographic features it cannot be distinguished from an osteoma or even a normal cortex.* **(Right)** *The bone tissue in melorheostosis is cortical-like in architecture and is composed of lamellar and woven bone. The osteoblasts and osteocytes tend to be inconspicuous and appear quiescent.*

Paget Disease of Bone



Low-Grade Osteosarcoma



**(Left)** *Although the bone is thickened in Paget disease, unlike melorheostosis that is composed of cortical-type bone, it does not have the appearance of cortical-type bone. There are prominent cement lines (mosaic pattern)* ⇨ *that are not seen in melorheostosis.* **(Right)** *Low-grade (parosteal) osteosarcoma arises on the surface of the bone; however, histologically, it is composed of spindle cells arranged in cellular fascicles covering the surfaces of long trabeculae of neoplastic bone, something not seen in melorheostosis.*

# Amyloidoma

KEY FACTS

## ETIOLOGY/PATHOGENESIS

- No identifiable underlying cause in primary amyloidosis
- Secondary amyloidosis develops in patients with underlying disorder, usually lymphoproliferative
  - Most commonly multiple myeloma: Amyloid light-chain protein deposits formed from immunoglobulin light chains

## CLINICAL ISSUES

- In tumoral amyloid deposition, there is focal deposition within skeleton, producing radiographic abnormality
- Amyloid deposition secondary to long-term dialysis is becoming more common (hemodialysis-associated amyloid)
- Patients on long-term hemodialysis can present with periarticular amyloid deposits
- Most patients with amyloidoma of bone have underlying plasmacytoma or plasmacytoid lymphoma
- Spine and skull most commonly involved
- Amyloid deposition can be disseminated or tumoral (focal)
- Presents with pain and sometimes pathologic fracture
- Patients on long-term hemodialysis can present with periarticular amyloid deposits

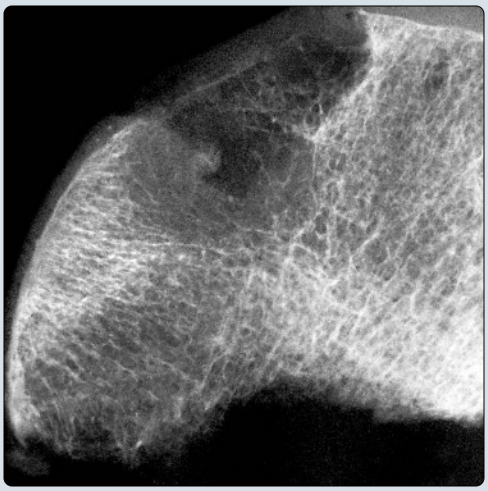
## ANCILLARY TESTS

- Congo red shows positive, diffuse staining pattern
- Amyloid deposit is reddish-orange by light microscopy
- Polarizing microscopy shows green birefringence, which is diagnostic for amyloid
- Cresyl fast violet shows positive, diffuse staining pattern
- Haphazardly arranged nonbranching amyloid fibrils
- Average diameter of fibrils ~ 9.0 nm (range: 7.5-10.0 nm)
- Ultrastructural features are same for all types of amyloidosis

**Amyloid Deposit in Femoral Head**

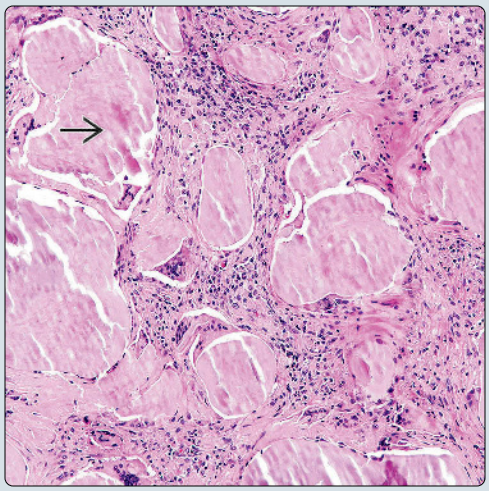


**Radiograph of Amyloid Deposit**

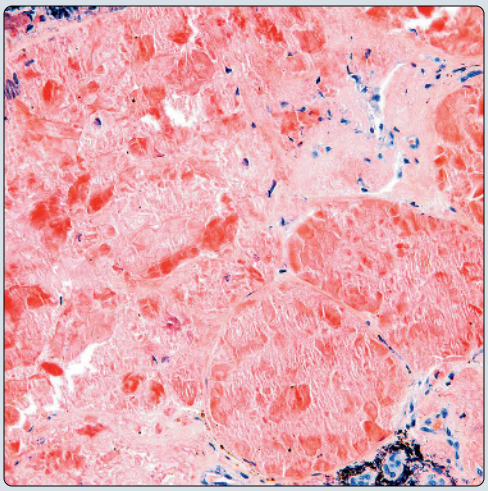


**(Left)** *Gross photograph shows a femoral head. A poorly circumscribed red lesion is identified beneath the articular cartilage. Histologically, this region showed abundant amyloid deposition.* **(Right)** *Specimen radiograph shows a resected head of femur. A subchondral lucent defect is present. Histologically, this region showed abundant amyloid deposition.*

**Giant Cell Reaction to Amyloid**



**Congo Red of Amyloid**



**(Left)** *In this low-power image of amyloidoma, the pink eosinophilic material represents amyloid ⇨. Note the giant cell reaction to amyloid.* **(Right)** *In this osseous amyloidoma, the extracellular material shows reddish-orange color on a Congo red stain. Under polarized light, the material demonstrates the characteristic apple-green birefringence.*

## TERMINOLOGY

### Synonyms

- Amyloid tumor

### Definitions

- Deposition of amyloid (proteinaceous substance) in bone

## ETIOLOGY/PATHOGENESIS

### Primary Amyloidosis

- No identifiable underlying cause

### Secondary Amyloidosis

- Develops in patients with underlying disorder, often lymphoproliferative disorder
  - Most commonly multiple myeloma: Amyloid light-chain (AL) protein deposits formed from immunoglobulin light chains
  - Can also occur in setting of chronic inflammatory conditions such as chronic osteomyelitis and tuberculosis: Amyloid A (AA) fibril protein deposition, rare type of amyloid
  - More recently, deposition of amyloid with β2-microglobulin protein has been seen in setting of long-term dialysis

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Tumoral amyloidosis (amyloidoma) of bone is rare
  - Amyloid deposition of tenosynovial tissue secondary to long-term dialysis is becoming more common (hemodialysis-associated amyloid)
- Age
  - Usually older individuals
    - Similar age as patients with plasmacytoma and plasmacytoid lymphomas
- Sex
  - More common in male patients

### Site

- Spine and skull most commonly involved

### Presentation

- Amyloid deposition can be disseminated or tumoral (focal)
  - In tumoral amyloid deposition, there is focal deposition within skeleton, producing radiographic abnormality
- Presents with pain and sometimes pathologic fracture
  - When it involves skull and spine, patients can present with neurologic symptoms
- Patients on long-term hemodialysis can present with periarticular amyloid deposits
  - Up to 50% of patients on long-term hemodialysis develop deposits within synovium, joints, and tendon sheaths
- Symptoms can be present from months to years

### Natural History

- Progression to disseminated disease common, with most patients dying within months or few years; most patients develop plasmacytomas or plasmacytoid lymphomas

## IMAGING

### Radiographic Findings

- Lytic, expanding lesion
- Margins may be well defined and sclerotic or ill defined

### MR Findings

- Demonstrates bone and soft tissue involvement, especially when spine involved
- May be low signal intensity on T1- and T2WI

### CT Findings

- Similar to MR, CT is helpful in demonstrating extent of lesion

### Bone Scan

- Increased uptake of radionucleotide

## MICROSCOPIC

### Histologic Features

- Amorphous, acellular eosinophilic deposits are seen within bone but can also be seen in walls of blood vessels
  - May be surrounded by histiocytic and giant cell reaction with lymphoplasmacytic infiltrate
  - May simulate corpora amylacea and become calcified, even ossified
- In hemodialysis-associated amyloid, deposition may be seen in paraarticular location

## ANCILLARY TESTS

### Histochemistry

- Congo red shows positive, diffuse staining pattern
  - Amyloid deposit is reddish-orange by light microscopy
  - Polarizing microscopy shows green birefringence, which is diagnostic for amyloid
- Cresyl fast violet shows positive, diffuse staining pattern

### Immunohistochemistry

- κ and λ staining in AL deposits
- Amyloid A protein in AA amyloid
- β2-microglobulin in β2-amyloid deposition

### Electron Microscopy

- Haphazardly arranged, nonbranching amyloid fibrils
- Average diameter of fibrils ~ 9.0 nm (range: 7.5-10.0 nm)
- Ultrastructural features are same for all types of amyloidosis

## DIAGNOSTIC CHECKLIST

### Pathologic Interpretation Pearls

- Most, if not all, AL amyloid deposits in bone are secondary to plasmacytomas or plasmacytoid lymphomas

## SELECTED REFERENCES


1. Mulleman D et al: Primary amyloidoma of the axis and acute spinal cord compression: a case report. Eur Spine J. 13(3):244-8, 2014
2. Pambuccian SE et al: Amyloidoma of bone, a plasma cell/plasmacytoid neoplasm. Report of three cases and review of the literature. Am J Surg Pathol. 21(2):179-86, 1997
3. Lai KN et al: Pathologic hip fractures secondary to amyloidoma. Case report and review of the literature. Am J Med. 77(5):937-43, 1984

# Gaucher Disease

KEY FACTS

## TERMINOLOGY

- Metabolic disease caused by mutations in gene encoding for glucocerebrosidase
  - Excessive accumulation of glucocerebrosides within reticuloendothelial system, including spleen, liver, and bone marrow
- 3 clinical types recognized: Types I, II, and III

## ETIOLOGY/PATHOGENESIS

- Autosomal recessive
- > 200 mutant alleles have been identified

## CLINICAL ISSUES

- Most common lysosomal storage disease
- Type I predominantly affects Jews of European descent
  - May have normal lifespan
- Types II and III have no ethnic predilection
- Symptomatic treatment
- Enzyme replacement therapy
- Substrate reduction therapy

## IMAGING

- Widening of distal femoral metadiaphysis: Erlenmeyer flask deformity
- Osteopenia and patchy calcified marrow infarcts
- Osteonecrosis

## MICROSCOPIC

- Diagnostic feature is Gaucher cells in bone marrow, spleen, liver
- Gaucher cells have abundant fibrillary, eosinophilic granular cytoplasm resembling crumpled paper

## TOP DIFFERENTIAL DIAGNOSES

- Prosthetic wear debris reaction
- Other metabolic diseases involving bone marrow

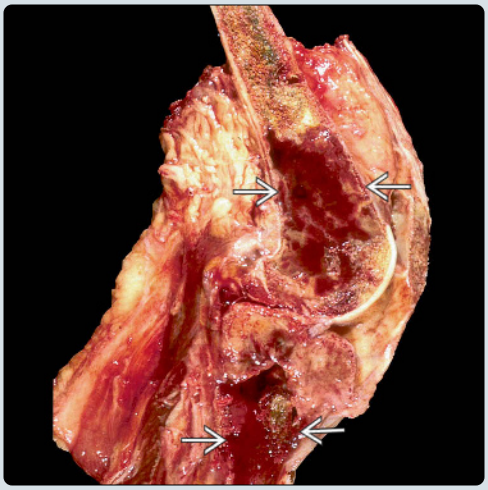
## DIAGNOSTIC CHECKLIST

- Gaucher cells infiltrating throughout marrow

**Lytic Lesion in Gaucher Disease**



**"Gaucheroma" in Femur and Tibia**

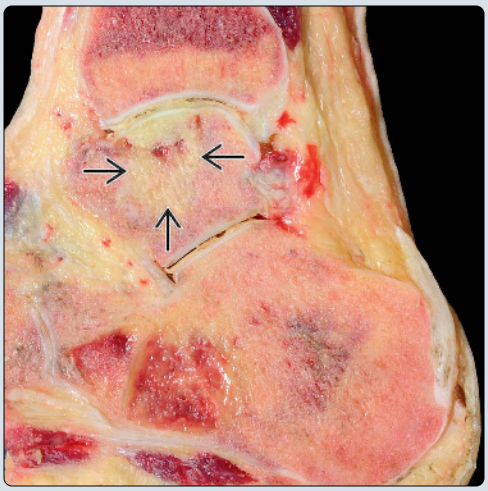


**(Left)** *Gaucher disease manifests as a loculated lucent lesion in the distal femur. The lesion is compartmentalized by septations that vary in thickness and has well-defined sclerotic margins. A subtle Erlenmeyer flask deformity is present.* **(Right)** *Gaucher disease presents as mass-like lesions in the femur and tibia in an adult patient, resulting in extensive localized bone loss. The lesions are soft, hemorrhagic, and irregular in contour.*

**Osteonecrosis**



**Osteonecrosis of Talus**



**(Left)** *Femoral head removed from a patient with Gaucher disease contains an area of osteonecrosis. The irregular area of necrosis is pale yellow and surrounded by a thin rim of gray tissue. The articular cartilage is starting to separate from the bone.* **(Right)** *This amputation from a patient with Gaucher disease shows osteonecrosis of the talus. The zone of necrosis appears as a pale yellow zone that abuts the base of the articular cartilage.*

## TERMINOLOGY

### Definitions

- Metabolic disease caused by mutations in gene encoding glucocerebrosidase on chromosome 1q22
  - Abnormal accumulation of glucocerebroside in macrophages within reticuloendothelial system especially bone marrow
  - Major source of substrate glucocerebroside is sphingolipids in cell membranes

## ETIOLOGY/PATHOGENESIS

### Genetic Disease

- Autosomal recessive
- > 200 mutations producing 3 major clinical types

## CLINICAL ISSUES

### Epidemiology

- Incidence
  - Most common lysosomal storage disease (1 in 20,000)
- Age
  - Depends on type, newborns or adults
- Ethnicity
  - Type I predominantly affects Jews of European descent
  - Types II and III have no ethnic predilection

### Presentation

- Varies according to type
- Type I: Nonneuronopathic form or adult form
  - Symptoms from splenomegaly and involved bone marrow
  - Affects histiocytes throughout body; no CNS disease
    - Predominantly involves spleen and skeleton
    - Skeletal involvement can lead to osteoporosis, fractures, and bone infarcts with pain ("bone crisis")
- Type II: Acute neuronopathic form
  - Also called infantile acute cerebral pattern
  - Absent glucocerebrosidase activity with progressive CNS involvement and early death
- Type III: Chronic neuronopathic form
  - Intermediate between types I and II
  - Neurologic symptoms are slowly progressive and appear later in childhood than in patients with type II
    - Patients may live into adulthood

### Treatment

- Symptomatic treatment
- Enzyme replacement therapy
  - Effective in type I with normal life expectancy
- Substrate reduction therapy

### Prognosis

- Type I
  - Progressive disease, usually normal life span
- Type II
  - Patients usually die during first 3 years of life
- Type III
  - Intermediate between types I and II

## IMAGING

### Radiographic Findings

- Widening of distal femoral metadiaphysis: Erlenmeyer flask deformity
- Avascular necrosis, especially proximal femur
- Osteopenia and patchy calcified marrow infarcts
- Vertebra can have central calcified bone infarct producing bone-in-bone appearance
- Lytic lesions

### MR Findings

- Early hip avascular necrosis
- Decreased marrow signal on T1- and T2-weighted images due to Gaucher cells
- Vertebral endplate collapse producing ballooning of disc

### CT Findings

- Vertebral collapse
- Hepatosplenomegaly when present

### Bone Scan

- Decreased uptake in bone infarcts

## MACROSCOPIC

### General Features

- Resected specimen may show spotty gray-yellow areas
- Resection usually done for avascular necrosis
  - Wedge-shaped yellow subchondral area with separation of overlying articular cartilage

## MICROSCOPIC

### Histologic Features

- Gaucher cells in bone marrow, spleen, liver, lymph nodes
- Gaucher cells have abundant fibrillary, eosinophilic granular cytoplasm resembling crumpled paper
  - Nucleus is centrally or eccentrically located
  - Cytoplasmic PAS(+) diastase resistant material

## ANCILLARY TESTS

### Electron Microscopy

- Elongated lysosomes with intralysosomal tubular structures

### Genetic Testing

- Carriers have germline mutations in blood or saliva

## DIFFERENTIAL DIAGNOSIS

### Prosthetic Wear Debris Reaction

- Florid histiocytic reaction to prosthetic components
- Wear debris present

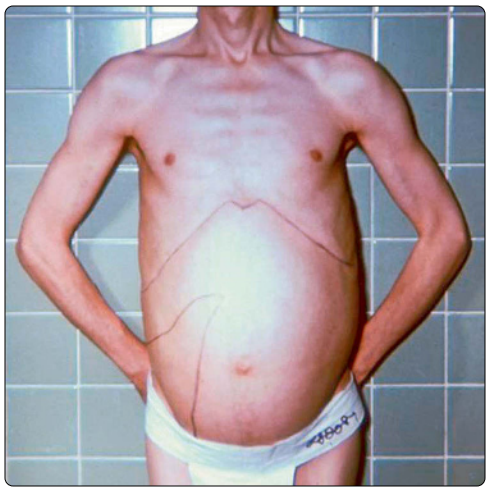
### Other Metabolic Bone Diseases

- Other metabolic diseases have diffuse histiocytic infiltration of marrow

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2. Baris HN et al: Gaucher disease: the metabolic defect, pathophysiology, phenotypes and natural history. Pediatr Endocrinol Rev. 12 Suppl 1:72-81, 2014

### Hepatosplenomegaly

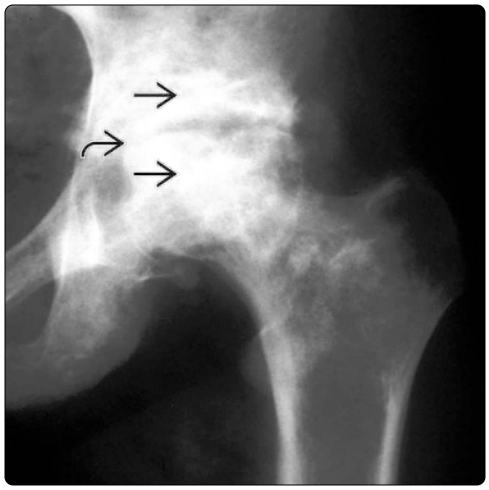


### Erlenmeyer Flask Deformity

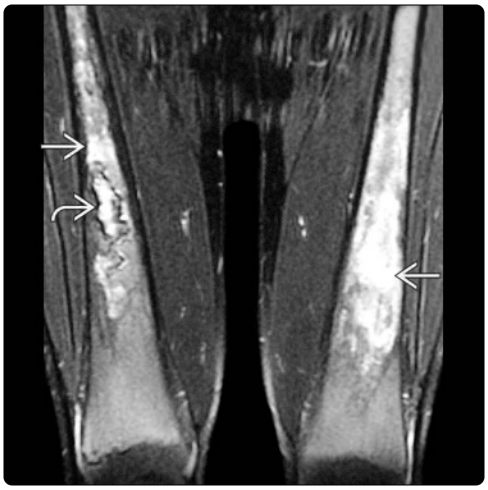


**(Left)** *An adult patient with Gaucher disease stands with markings on his abdomen that demonstrate the extent of his enlarged liver and spleen. Hepatosplenomegaly is a common finding in this disease. The organomegaly is caused by infiltration by Gaucher macrophages.* **(Right)** *Gaucher disease presents with Erlenmeyer flask deformity of the distal femurs ➔ with increased density ⇨ of the intramedullary bone. There is also a modeling deformity of the proximal tibiae.*

### Osteonecrosis



### Bone Marrow Infarcts

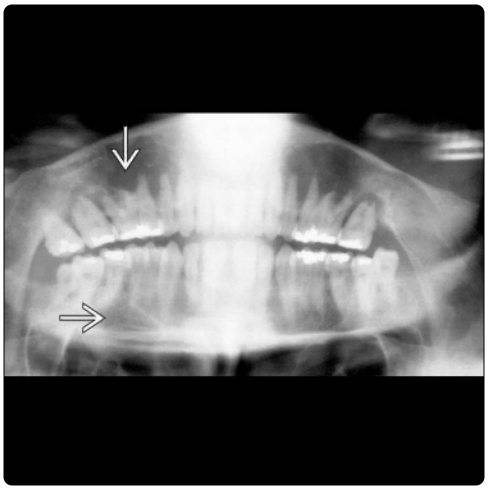


**(Left)** *Gaucher disease associated osteonecrosis of the femoral head producing flattening of the head with subchondral sclerosis that also affects the acetabulum ⇨ is shown. The joint space is narrowed ⇨, and osteophytes are present, indicative of secondary osteoarthrosis.* **(Right)** *Coronal T2-weighted image with fat saturation shows extensive marrow necrosis ➔ in Gaucher disease. The dark signal along the margins of the areas of necrosis ➔ (reactive ossification) is better seen on the right.*

### Pathological Fracture

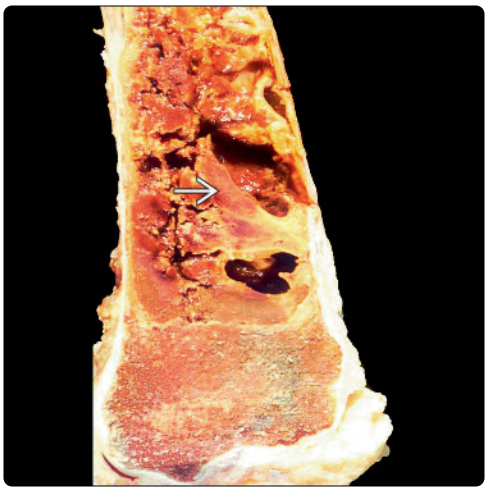


### Gaucher Disease of Jaw

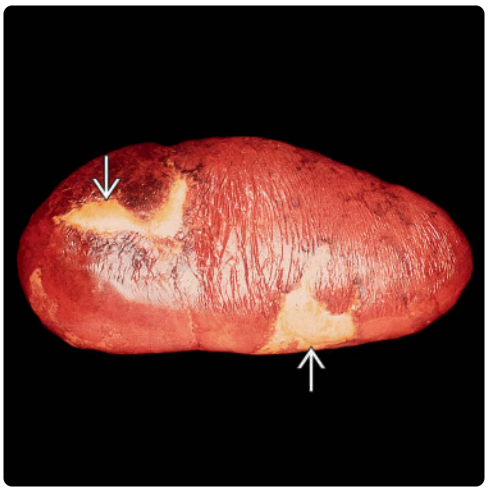


**(Left)** *Pathologic fracture ⇨ through a mixed lucent and sclerotic lesion is shown in the mid and distal femoral shaft. The lesion is caused by a tumor-like aggregate of Gaucher macrophages.* **(Right)** *Panorex view of the jaws shows lucent lesions ➔ within the mandible and maxilla with floating teeth. The individual teeth are unremarkable. These changes are characteristic of Gaucher disease and can be the presenting findings in an otherwise asymptomatic patient.*

### Mass of Gaucher Cells Destroying Bone

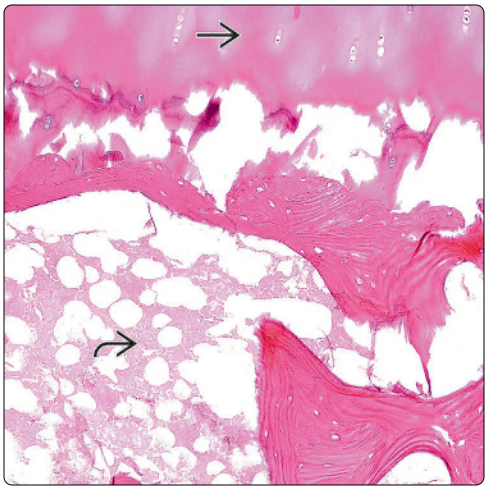


### Splenomegaly and Infarcts

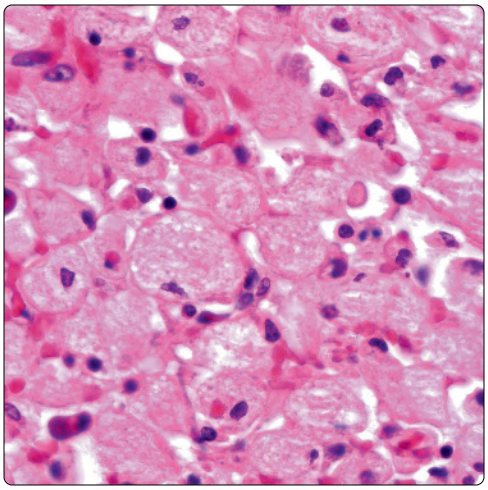


**(Left)** *Sagittal section of the distal femur in an adult patient with severe Gaucher disease shows a mass-like "gaucheroma" ➡. The lesion is soft, friable, and brown-red in color, replaces the normal marrow, and has produced significant destruction of the cancellous bone and thinning of the cortex.* **(Right)** *Resected intact enlarged spleen from an adult patient with Gaucher disease contains irregular pale regions ➡, which represent areas of previous infarctions.*

### Osteonecrosis

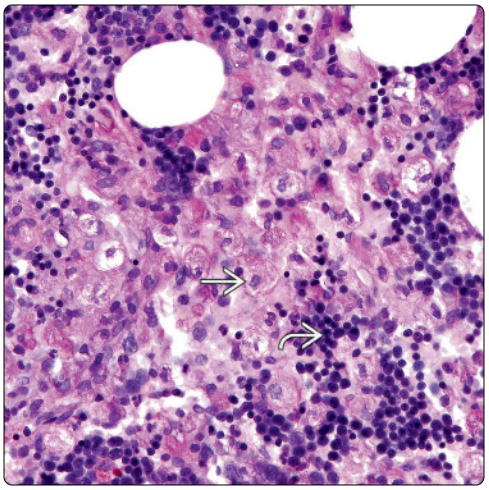


### Gaucher Cells

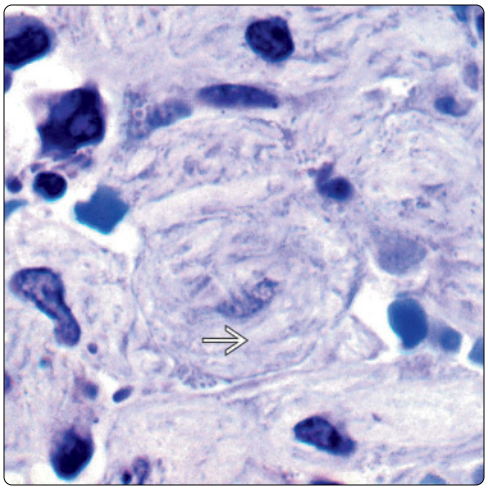


**(Left)** *Osteonecrosis is a common complication in Gaucher disease. In this example, the articular hyaline cartilage ⇨ remains viable, whereas the cancellous bone and hematopoietic marrow ⇨ is necrotic. Careful examination of the necrotic marrow cells reveals those with the size and configuration of Gaucher cells.* **(Right)** *Gaucher macrophages are polyhedral and contain abundant eosinophilic cytoplasm that may appear vacuolated or fibrillar, resembling wrinkled tissue paper.*

### Gaucher Cells in Marrow



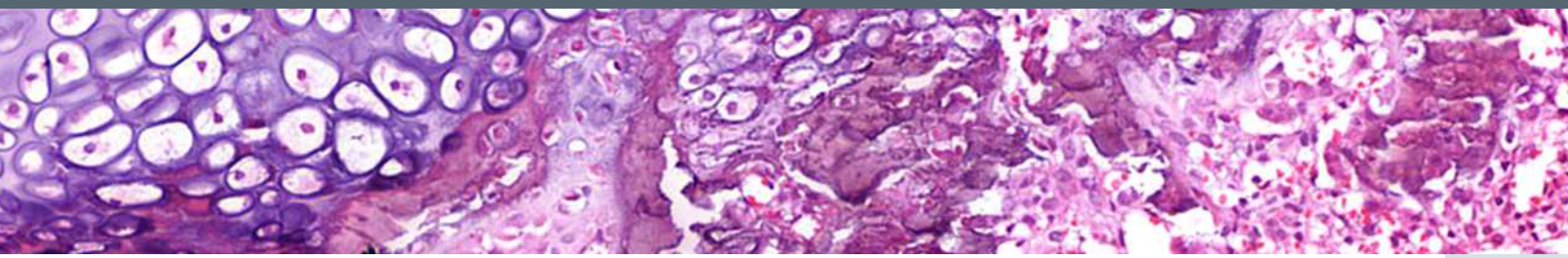
### Gaucher Cell With Fibrillar Cytoplasm



**(Left)** *Gaucher macrophages contain glucocerebrosides within the lysosomes in their cytoplasm. These substances stain with PAS diastase and are reddish magenta in color ➡. In this case, the Gaucher cells are admixed with coexisting hematopoietic elements ⇨.* **(Right)** *Gaucher cells are filled with sphingolipids that engorge cytoplasmic lysosomes. The lysosomes cause the cytoplasm to have a fibrillar appearance resembling wrinkled tissue paper ➡.*

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